Chief Review Officer Patrick Massad
patrickm@paab.ca

Menu “du Jour”

Perceptions of change Vs Actual change

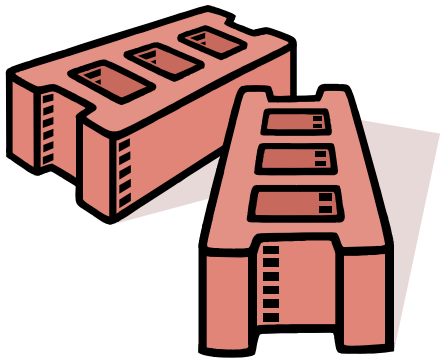
Perception

- Advertising Vs Non-Advertising
  - – PAAB preclearance Vs exempt from preclearance

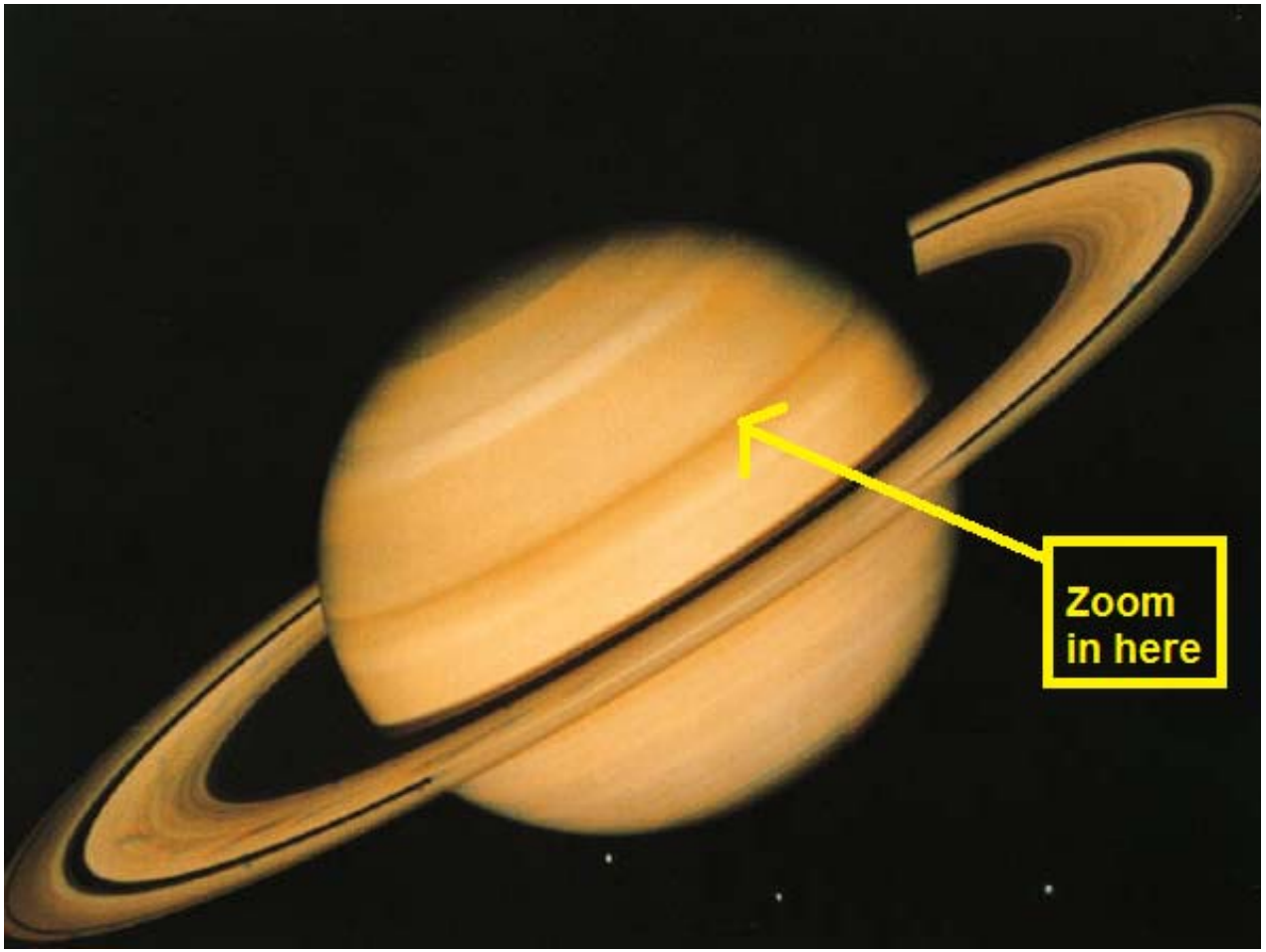
Reality

- Code revision
  - –PI & fair balance, evidence standards, online activities, over the counter & natural health products

Sometimes change is real



Sometimes it's just perceived


Zoom
in here

Kanada: A place like no other

* Not actual size of Kanada

About Kanada

Population: 15000 (humans)

Agriculture accounts for 70% of GDP*

*Gross Domestic Product

Farming is a regulated industry

FDA section 9.1 (FDA= Farm and Dairy Act)

Farms raising animals for commercial purposes are required to be inspected on a monthly basis to ensure that:

- the barn is clean
- the animals are processed in a manner preventing contamination

So, when it comes to farming…

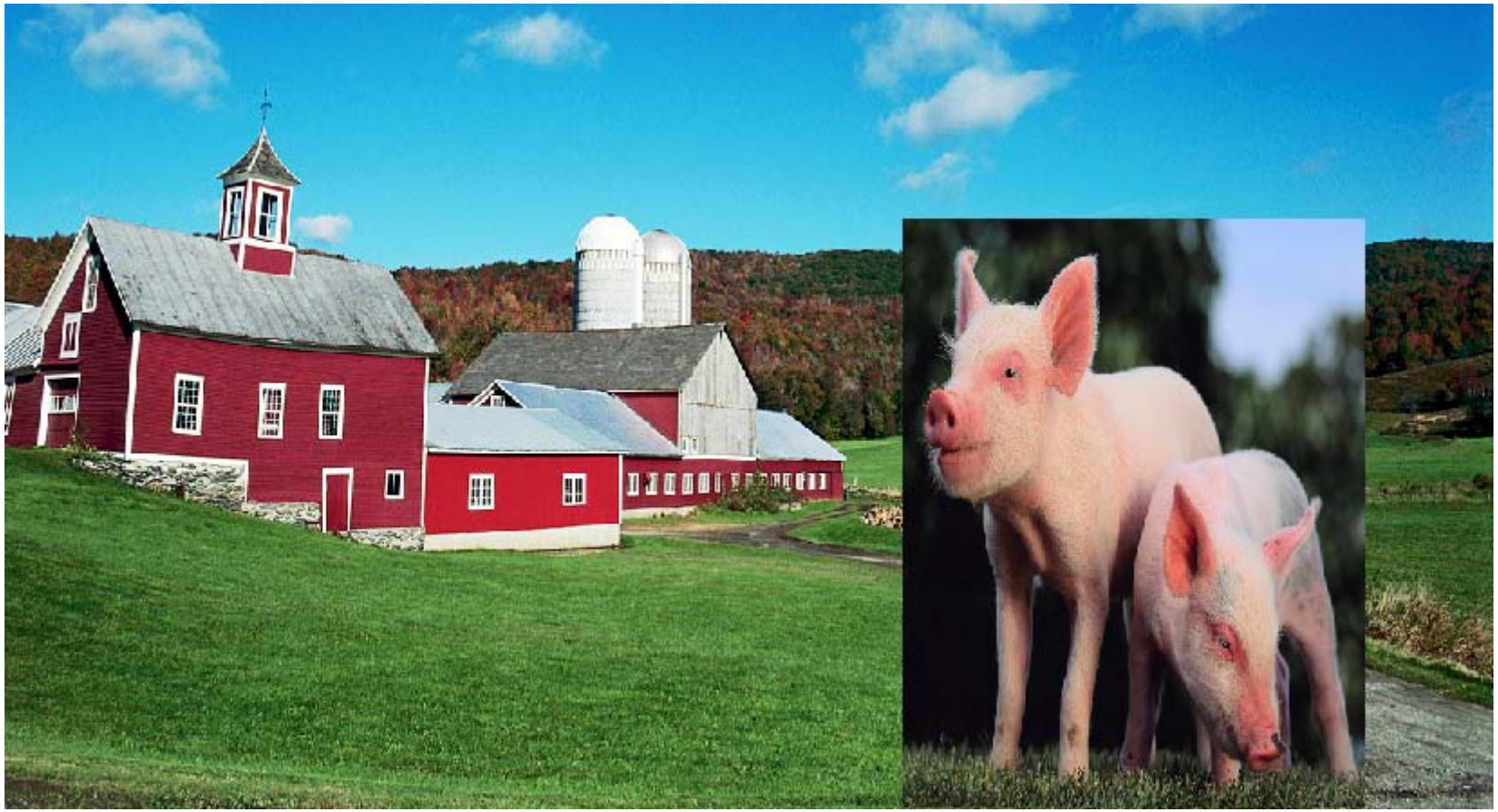
If it's for commercial purposes, it's regulated

*Fictitious case. May not be representative of anything at all.

Kanada: Home of 500 Farms

Shakespeare's Farm

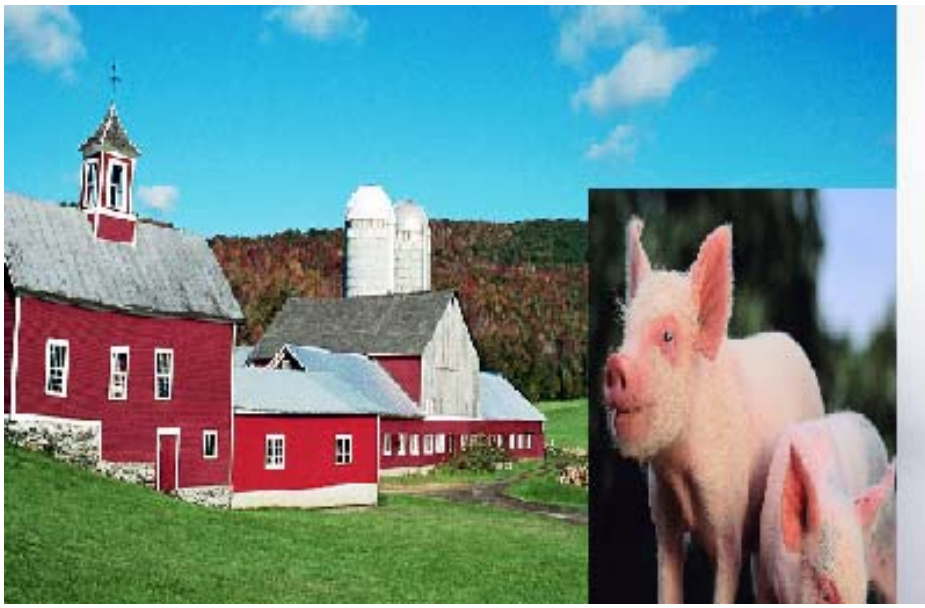
Klinton's Farm



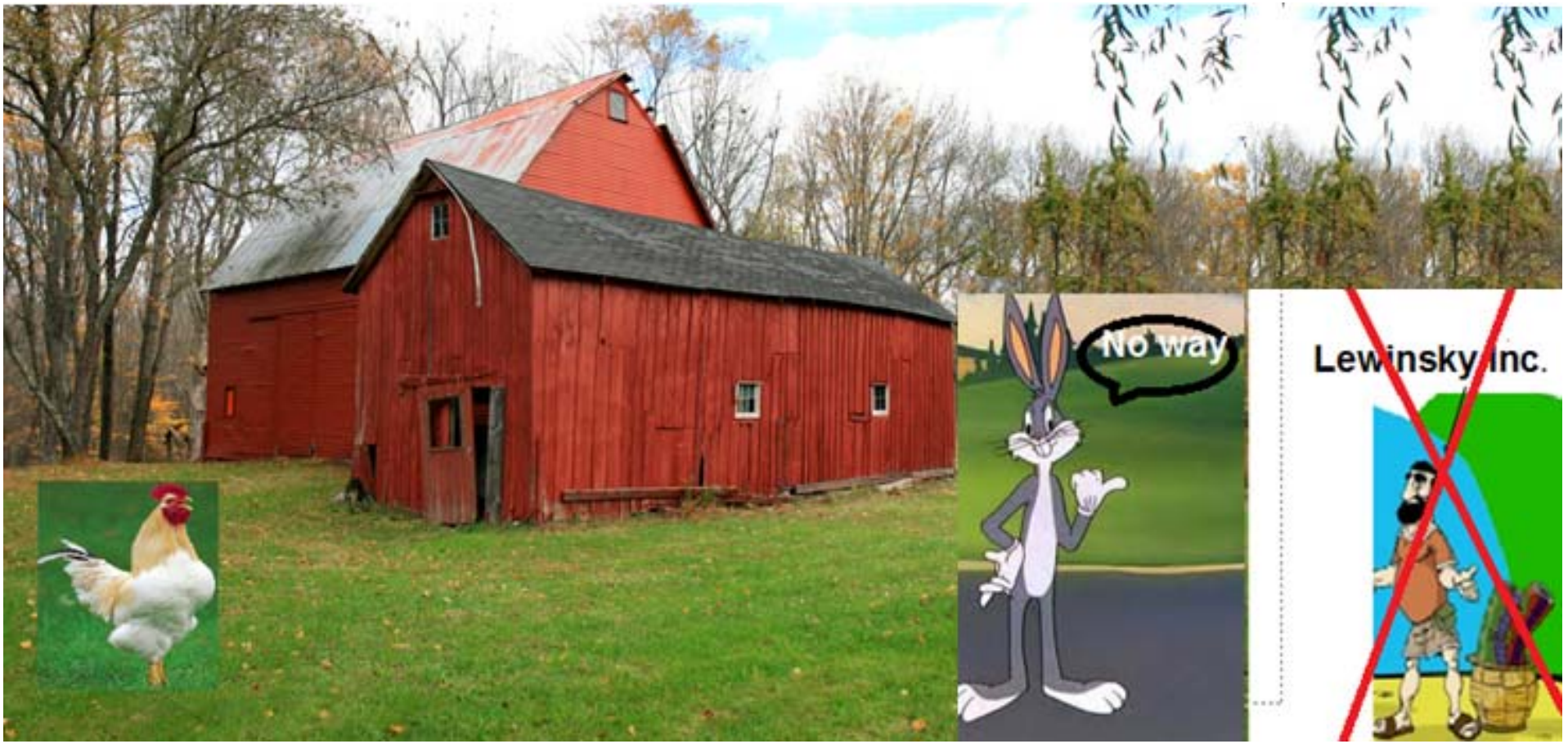
Bugs Bunny's Farm

Shakespeare's Farm

Klinton's Farm



Bugs Bunny's Farm



Bugs Bunny had already consulted the regulators about a similar opportunity a few years ago

When approached by the regulators:

Regulators Issued Guidance

Klinton and many others informed the regulators that additional guidance in defining “commercial activities” was needed.

The regulators issued a document clarifying that although bartering is legal in Kanada, it is a commercial activity (and monthly farm inspections are required).

Many farm owners where confused as to why the “rules were changing”.

What changed ?

Did the regulations really change ?

- Change Vs Clarification

Perception Vs Reality

- “It’s new” Vs “It’s new to me”

Back to the real world

- Last quarter of 2010:
  - In response to complaints from within the industry, PAAB sent 8 monitoring notices involving alleged paid editorial articles by pharma companies.
  - These were deemed to be advertising
  - Contained:
    - Off-label content
    - Unapproved drugs
    - Comparisons based on poor evidence
    - No balance with respect to risk information

- December 8, 2010: PAAB received advisory opinion from Health Canada

- The monitoring letters triggered multiple in house workshop requests. Clients asked for a tool that could complement the Health Canada "Distinction Between Advertising and Other Activities" document.

- PAAB has been working on this tool and adapting it based on ongoing consultation (i.e. a decision tree). If you'd like a chance to provide comments, email me: patrickm@paab.ca

Is this advertising ?

Who cares ? ?

Brace yourself !!

If it is advertising the advertising regulations apply...

Irrespective of the educational usefulness of the material/activity.

Food and Drugs Act and Regulations

- No person shall … advertise a new drug unless…the Minister has issued a Notice of Compliance to the manufacturer of the new drug… (FDA c.08.002)

- No person shall … advertise any drug in a manner that is false, misleading or deceptive or is likely to create an erroneous impression regarding its character, value, quantity, composition, merit or safety. (section 9.(1))

Health Canada definition of advertising

"any representation by any means whatever for the purpose of promoting **directly or indirectly** the sale or disposal of any food, drug, cosmetic or device"

-section 2 of Food Drugs Act

Health Canada guidance document "The Distinction Between Advertising and Other Activities":

- What is the **context** in which the message is disseminated ?
- Who are the primary and secondary **audience**s ?
- **Who delivers** the message (the provider) ?
- Who **sponsors** the message and how ?
- What **influence** does the drug manufacturer have on the message content ?
- What is the **content** of the message ?
- With what **frequency** is the message delivered ?

"No one factor in itself will determine whether or not a particular message is advertising."

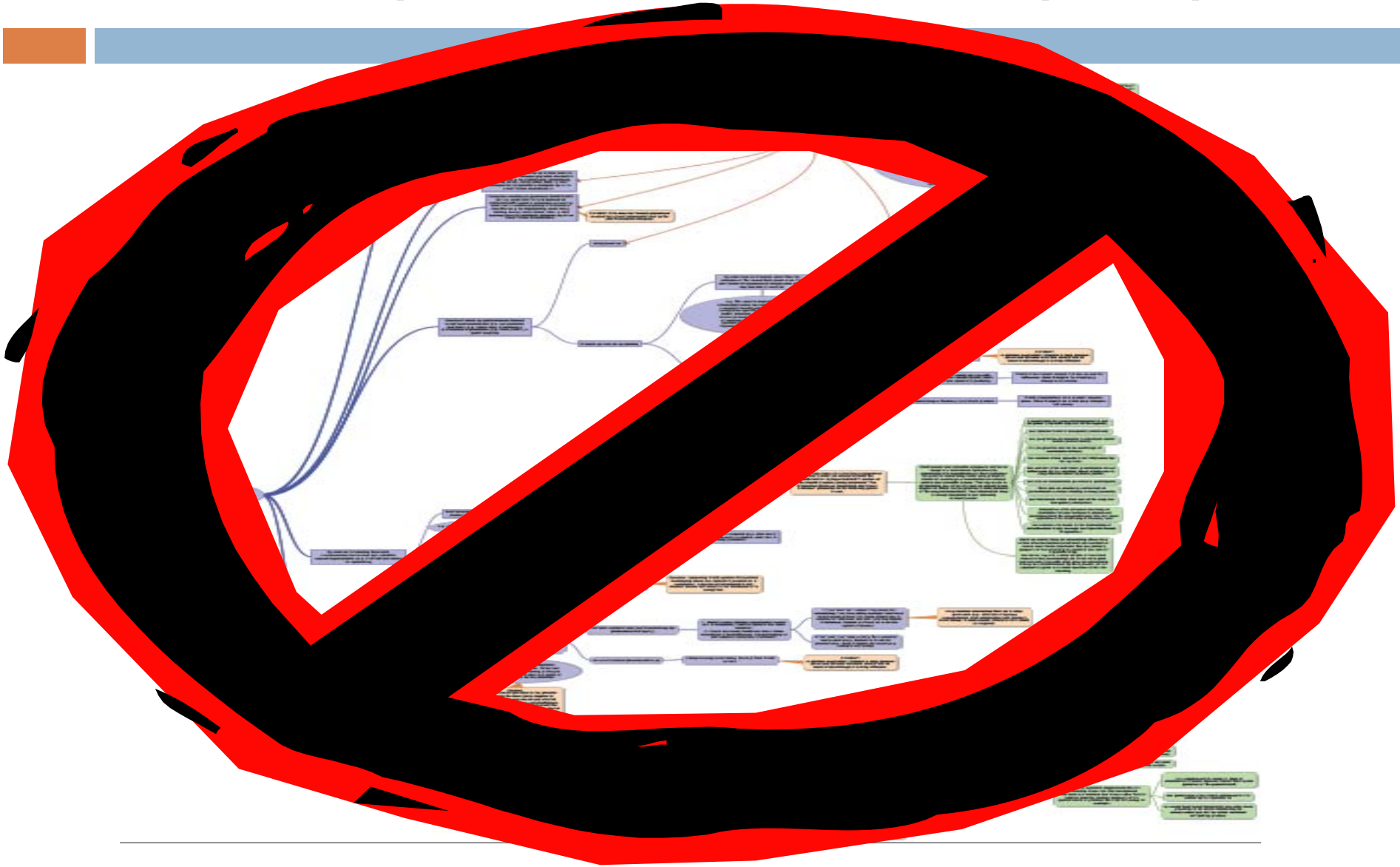
…If uncertain, don't hesitate to ask PAAB.

We'll respond to requests for written opinions within 4 days.

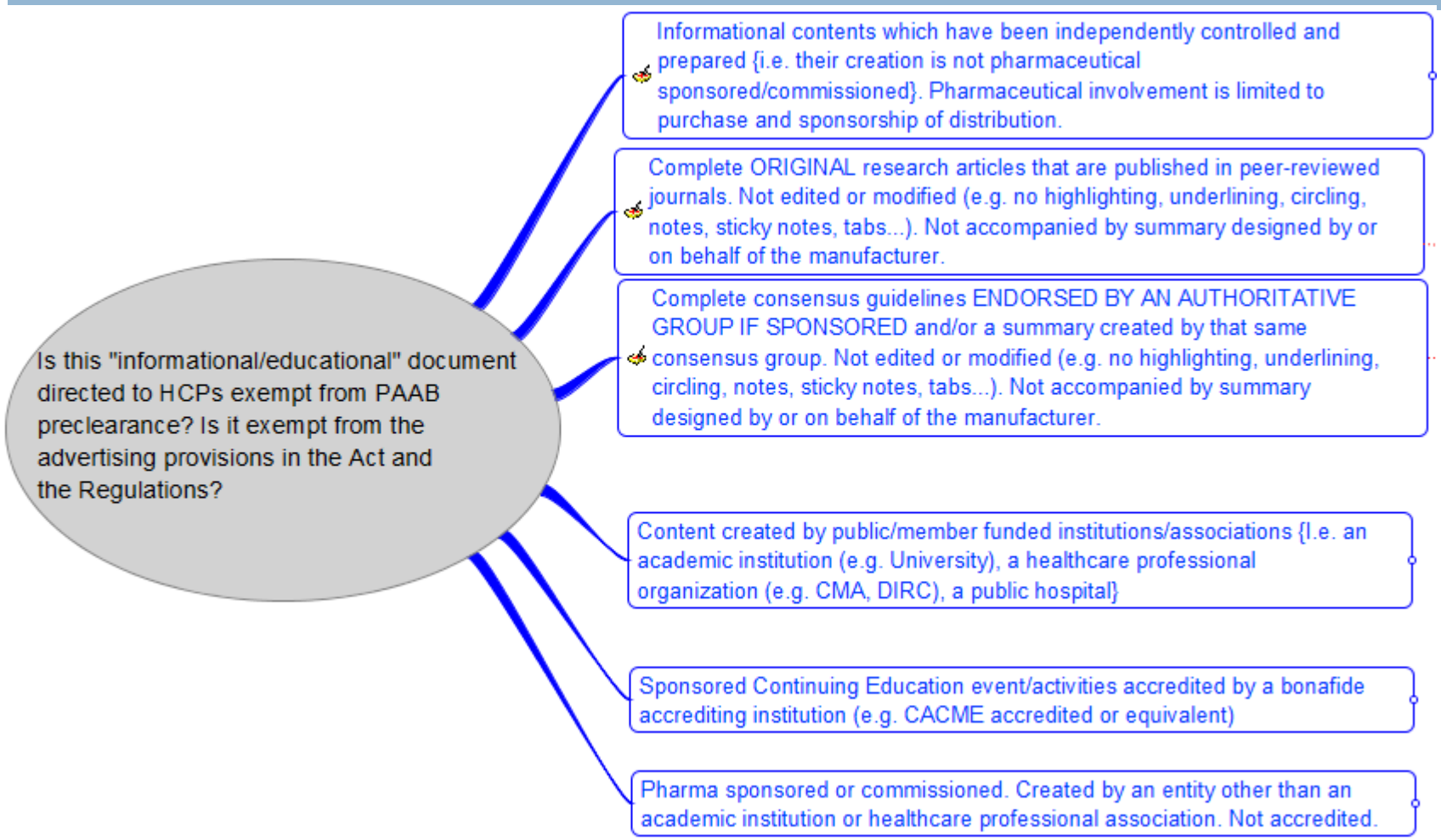
Confused ? ?

Let's SIMPLIFY…

We'll find peace of mind in simplicity:



New Format


Is this "informational/educational" document directed to HCPs exempt from PAAB preclearance? Is it exempt from the advertising provisions in the Act and the Regulations?
Informational contents which have been independently controlled and prepared {i.e. their creation is not pharmaceutical sponsored/commissioned}. Pharmaceutical involvement is limited to purchase and sponsorship of distribution.
Complete ORIGINAL research articles that are published in peer-reviewed journals. Not edited or modified (e.g. no highlighting, underlining, circling, notes, sticky notes, tabs...). Not accompanied by summary designed by or on behalf of the manufacturer.
Complete consensus guidelines ENDORSED BY AN AUTHORITATIVE GROUP IF SPONSORED and/or a summary created by that same consensus group. Not edited or modified (e.g. no highlighting, underlining, circling, notes, sticky notes, tabs...). Not accompanied by summary designed by or on behalf of the manufacturer.
Content created by public/member funded institutions/associations {I.e. an academic institution (e.g. University), a healthcare professional organization (e.g. CMA, DIRC), a public hospital}
Sponsored Continuing Education event/activities accredited by a bonafide accrediting institution (e.g. CACME accredited or equivalent)
Pharma sponsored or commissioned. Created by an entity other than an academic institution or healthcare professional association. Not accredited.

Breaking down the 7 questions.
2 separate groups of factors

1. **Content & creation factors:**
   - What is the content ?
     - drug Vs disease
     - emphasis on a product ?
     - would a competitor want to sponsor the same material/activity* ?
     - would the content lead someone to deduce that the material was sponsored by the market authorization holder without even reading the transparency disclaimer
   - Who sponsors the message and how ?
     - What is sponsored? (content creation Vs distribution)
   - Extent of drug manufacturer influence over message content ?
     - None Vs author selection, specific focus of content or scope of research, review privileges…

2. **Distribution and/or availability factors**
   - Audience ?
   - Context of dissemination ?
   - Who delivers ?
   - Frequency of delivery ?

*e.g. Unlikely if emphasises the benefits of the market authorization holder's products or if it implies superiority over other treatment options.

Content which would otherwise not be considered advertising **can be rendered subject to the advertising regulations** by the distribution and/or availability factors!!

A change in one of these factors should **trigger re-assessment of whether it is advertising**. When this occurs, the content should undergo preclearance unless exemptions from PAAB code s6.6 are met.

4 buckets cover much of the landscape

- **Independently controlled and prepared with pharmaceutical involvement limited to purchase and sponsorship of distribution?**
- **Original research articles published in peer-reviewed journals?**
- **Consensus guidelines endorsed by an authoritative group?**

Content created by a public/member funded institution/association or a HCP organization

Accredited Sponsored CHE

Pharma sponsored or commissioned. Created by entity other than an academic institution or healthcare professional association. Not accredited.

- **Independently controlled and prepared with pharmaceutical involvement limited to purchase and sponsorship of distribution?**
- **Original research articles published in peer-reviewed journals?**
- **Consensus guidelines endorsed by an authoritative group?**

Exempt from PAAB preclearance.

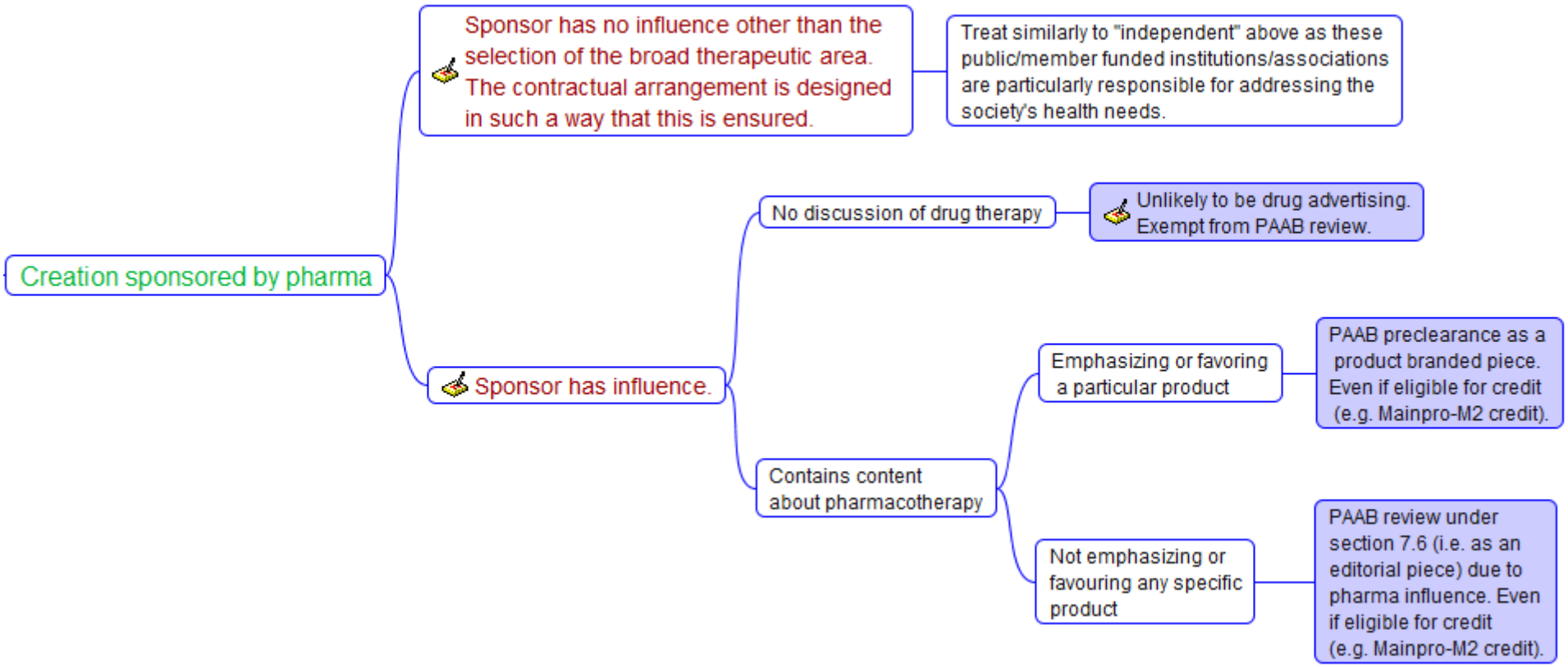
BUT…

may still fall under the definition of advertising.

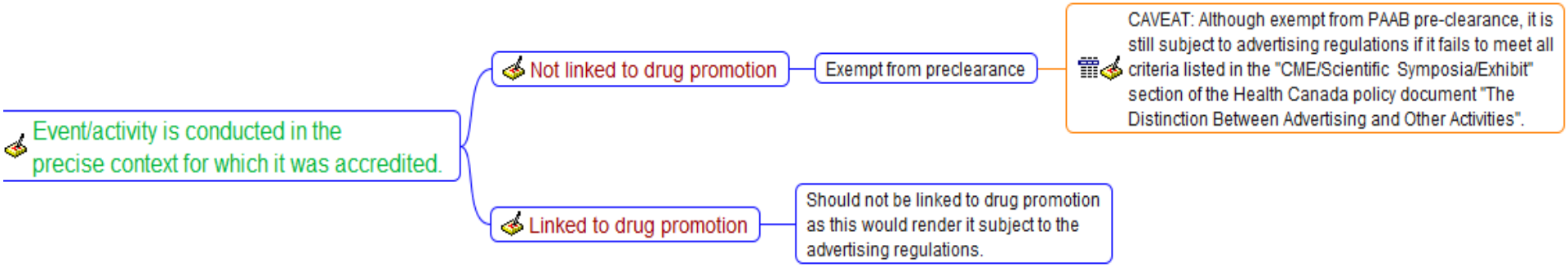
Consider Distribution and/or Availability factors

Content created by a public/member funded institution/association or a HCP organization

Exempt from preclearance if creation is not sponsored by pharma



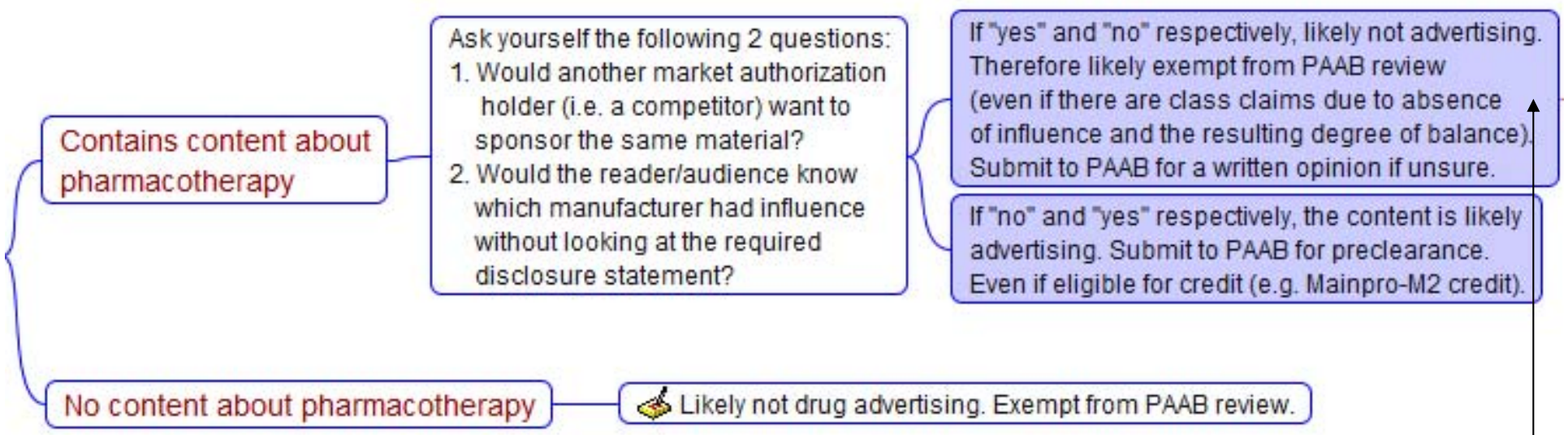
Accredited Sponsored CHE



Consider factors of distribution and/or availability:
Unsolicited distribution by sponsor (in part or whole) to a broader audience (e.g. slides or video recording) would requires PAAB review if it emphasizes or favours the sponsor's product.
Even if eligible for CE credit (e.g. Mainpro-M2 credit).

Pharma sponsored or commissioned. Created by entity other than an academic institution or healthcare professional association. Not accredited.

If sponsor has **no** influence over content or process…

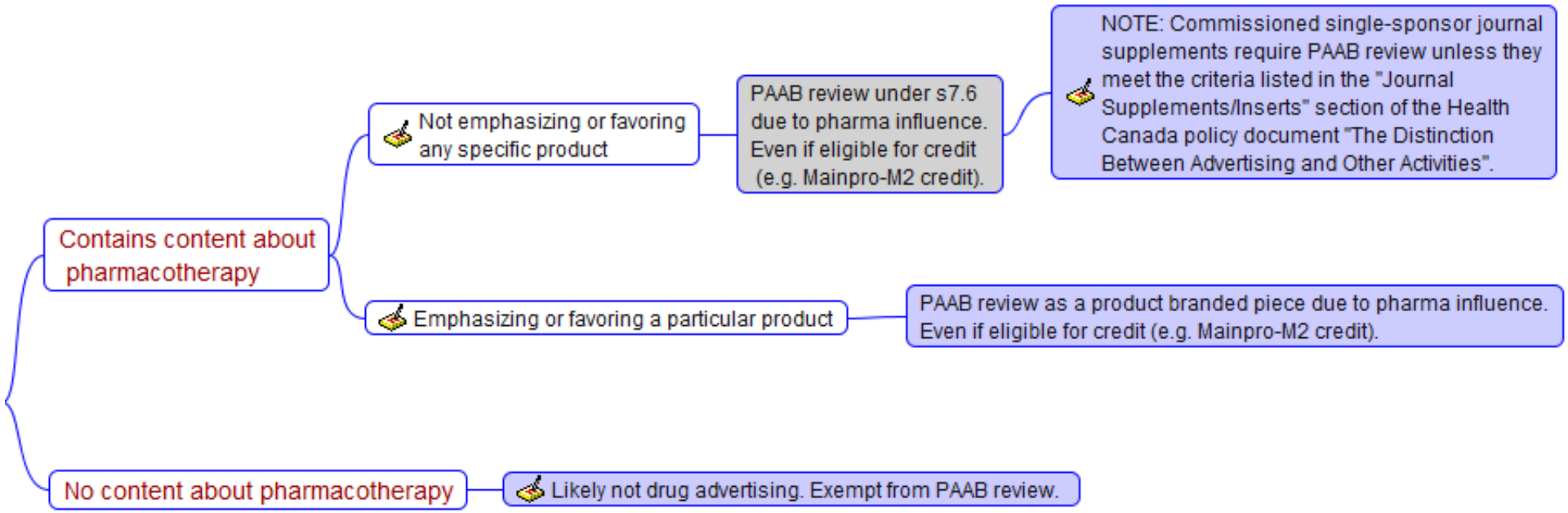


Consider factors of distribution and/or availability:

e.g. Rendered subject to the advertising regs if linked to advertising/promotion. In such cases, criteria for exemption from PAAB review are not met (i.e. not independent).

Pharma sponsored or commissioned. Created by entity other than an academic institution or healthcare professional association. Not accredited.

If sponsor has influence over content or process...

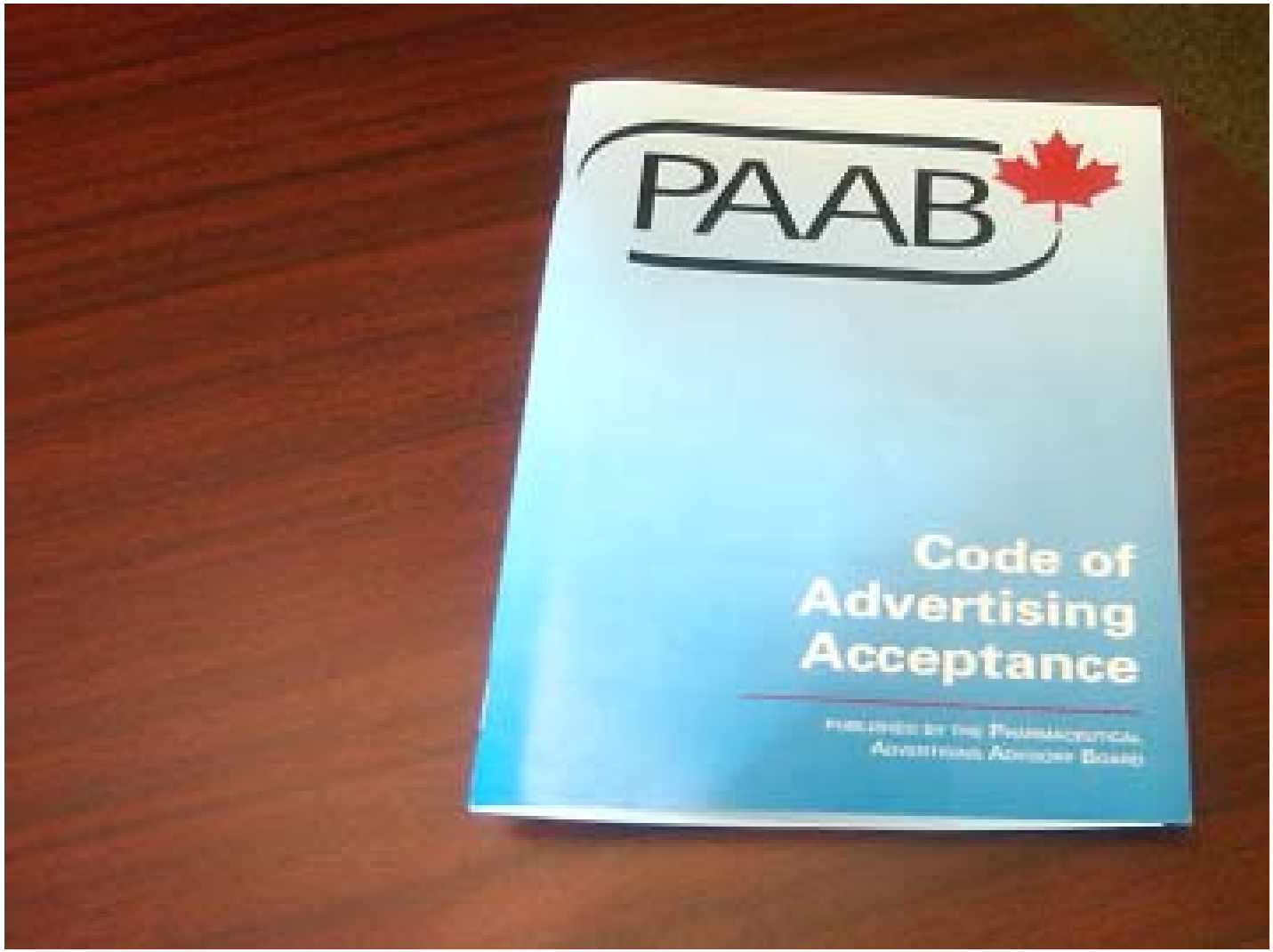


Perception Vs Reality

PAAB is working on a decision tree to help the industry use/interpret:

- the Health Canada “Distinction” document
- the current section 6.6 of the PAAB code

Moving on to the proposed code changes…



Code Review

The four major areas are:

- Product Information and Fair Balance
- Evidence for Claims
- Online Marketing Activities to Health Care Professionals and Direct-to-Consumer
- Nonprescription (OTC) and Natural Health product Advertising Requirements

Also inviting industry to suggest additional code sections which should be revisited

- PAAB has struck four expert advisory committees that provided recommendations for revision.
  - These committees are largely comprised of experts from within this industry (i.e. drug manufacturers, agencies/suppliers, publishers)
  - Others: HCPs, lawyers, PAAB

- Those recommendations are presently getting vetted through the PAAB stakeholders via survey.

Consultation: Have You Heard ?

- Over one thousand emails informing stakeholders about the consultation process
  - Last week of January emails were sent to inform that all content relating to the proposed code has been posted on PAAB website
- Surveys
  - Sent first week of February
  - The survey will only allow for one person within each organization to respond
    - To ensure interdepartmental collaboration for a single, unified response
  - Are YOU involved? Find out who is coordinating your company's response
    - If this is not apparent, contact Marla Weingarten
- Companies and organizations had to register with our external project manager.
  - This keeps the survey results **anonymous** to PAAB staff

Why did consultation begin in Jan 2012 ?

- Needed Research reports to feed into the expert committees to shape the proposed changes
  - Completed in December 2011
- Goal for a single set of code changes (rather than a sequential changes)
  - Goal: PAAB Board approval on August 24th
- Goal for the consultation process to include all proposed changes (rather than sequential changes)

Why August 24th target for approval ?

- Publishers require implementation of PI change at beginning of year for rate cards
  - Goal: implementation Jan 2013
- Communications program about the revisions in the Fall 2012
  - PAAB staff training
  - Client training

What needs to occur between today and Aug 24th, 2012?

- Survey deadline March 15th, 2012
- Analyse survey results for common ground and areas of difference by consultant.
  - PAAB staff will only see aggregated data
- Send draft 1 of Code to the PAAB Board and Health Canada (HC)
- Obtain comments re: draft 1 from PAAB Board and Health Canada
- Incorporate comments from PAAB Board and HC and send draft 2 of code
- Obtain comments re: draft 2 from PAAB Board and HC
- Disseminate final code revisions to the PAAB Board and Health Canada to review prior to vote
- Approval of the new PAAB code by vote via electronic meeting
  - It takes a two-thirds majority vote to change the code.

PAAB's Board of Directors

- Four pharmaceutical **trade associations**
  - Rx&D, BIOTECanada, CHPC, CGPA
- **Health professionals**
  - CMA, CPhA, FMSQ, AFMC
- **Patients**
  - Best Medicines Coalition (BMC)
  - Consumers Council of Canada (CCC)
  - Canada's Assoc for the Fifty-Plus (CARP)
- Can Assoc of Medical **Publishers** (CAMP)
- **Advertising industry** (AMAA)
- Chair, Vice-Chair, Treasurer

Product information (PI) s7 & Fair Balance

PI – PAAB Code s7

Currently:

"PI (when required) must be attached to the presentation or be distributed with it"

What is a PI ?

ARBACE
arbarsartan sodium

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Angiotensin II Receptor Antagonist

INDICATIONS AND CLINICAL USE:

Hypertension

ARBACE® (arbsartan sodium) is indicated for the treatment of essential hypertension.

ARBACE may be used alone or concomitantly with thiazide diuretics and should normally be used in those patients in whom treatment with diuretics or beta-blockers was found ineffective or has been associated with unacceptable adverse effects. ARBACE can also be tried as an initial agent in those patients in whom the use of diuretics and/or beta-blockers is contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects.

The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors have not been established.

Type 2 Diabetic Patients with Proteinuria and Hypertension

ARBACE is also indicated to delay the progression of renal disease as measured by the occurrence of doubling of serumcreatinine, and end stage renal disease, and to reduce proteinuria.

CONTRAINDICATIONS: ARBACE (arbsartan sodium) is contraindicated in patients who are hypersensitive to any component of this product.

ARBACE should not be used in pregnant women.

Use in Nursing Mothers

It is not known whether arbsartan or its active metabolite are excreted in human milk, however significant levels of both of these compounds have been shown to be present in the milk of lactating rats. Because many drugs are excreted in human milk, and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

Use in Children

Safety and effectiveness have not been established.

Use in the Elderly

No overall differences in safety were observed between elderly and younger patients, but appropriate caution should nevertheless be used when prescribing to elderly, as increased vulnerability to drug effect is possible in this patient population.

Safety Information

WARNINGS

Pregnancy

Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, ARBACE (arbsartan sodium) should be discontinued as soon as possible.

The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death.

Animal data: Arbsartan sodium has been shown to produce adverse effects in rat fetuses and neonates, which include decreased body weight, mortality and/or renal toxicity. Significant levels of arbsartan and its active metabolite were shown to be present in rat milk. Based on pharmacokinetic assessments, these findings are attributed to drug exposure in late gestation and during lactation.

Hypotension

Occasionally, symptomatic hypotension has occurred after administration of arbsartan, in some cases after the first dose. It is more likely to occur in patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

PRECAUTIONS

Hypersensitivity

Angioedema (see ADVERSE REACTIONS).

Renal Impairment

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been reported in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of arbsartan should include appropriate assessment of renal function.

Hyperkalemia

In a clinical study conducted in patients with type 2 diabetes with proteinuria and hypertension, the incidence of hyperkalemia was higher in the group treated with ARBACE (11%) as compared to the placebo group (5.4%), however, few patients discontinued therapy due to hyperkalemia. Careful monitoring of serum potassium is recommended.

Hepatic Impairment

Based on pharmacokinetic data which demonstrate significantly increased plasma concentrations of arbsartan and its active metabolite in cirrhotic patients after administration of ARBACE (arbsartan sodium), a lower dose should be considered for patients with hepatic impairment, or a history of hepatic impairment.

ADVERSE REACTION SERIOUSNESS AND INCIDENCE (see full listing):

ARBACE (arbsartan sodium) has been evaluated for safety in more than 5000 patients treated for essential hypertension. Of these, 3085 were treated with arbsartan monotherapy in controlled clinical trials. In open studies, over 2400 patients were treated with arbsartan for more than 6 months, and over 1200 for more than one year.

In controlled clinical trials, discontinuation of therapy due to clinical adverse experiences occurred in 3.8% and 4.0% of patients treated with ARBACE and placebo, respectively.

The following potentially serious adverse reactions have been reported rarely with arbsartan in controlled clinical trials: syncope, hypotension. In these controlled clinical trials for essential hypertension, dizziness was the only adverse experience, occurring in more than 1% of cases, that was reported as drug-related, and that occurred at a greater incidence in arbsartan-treated (2.4%) than placebo-treated (1.3%) patients. In double-blind, controlled clinical trials for essential hypertension, the following adverse reactions were reported with ARBACE at an occurrence rate of less than 1%, regardless of drug relationship: orthostatic effects, somnolence, vertigo, epistaxis, tinnitus, constipation, malaise, rash.

What is a PI ? continued . . .

ARBACE® was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria and hypertension. The most common drug-related side effects were asthenia/fatigue, dizziness, hypo tension and hyperkalemia (see PRECAUTIONS, Hyperkalemia).

Drug Interactions
Antihypertensive effect of arbsartan may be attenuated by the non-steroidal anti-inflammatory drug indomethacin.

Diuretics
Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with ARBACE. The possibility of symptomatic hypotension with the use of ARBACE can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of arbsartan. No drug interaction of clinical significance has been identified with thiazide diuretics.

Agents Increasing Serum Potassium
Concomitant use of potassium-sparing diuretics (e.g., spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium. Since ARBACE decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution.

Lithium Salts
As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered.

Digitalis
In 20 healthy volunteers, when a single oral dose of 0.5 mg digoxin was administered to patients receiving arbsartan for 7 days, digoxin AUC and digoxin Cmax ratios, relative to placebo, were found to be 1.2 and 1.38, respectively. The effect of arbsartan on steady-state pharmacokinetics of cardiac glycosides is not known.

Warfarin
Arbsartan administered for 7 days did not affect the pharmacokinetics or pharmacodynamic activity of a single dose of wartarin. The effect of arbsartan on steady-state pharmacokinetics of warfarin is not known.

Drugs Affecting Cytochrome P450 System
Rifampin, an inducer of drug metabolism, decreases the concentrations of the active metabolite of arbsartan. In humans, two inhibitors of P450 3A4 have been studied. Ketoconazole did not affect the conversion of arbsartan to the active metabolite after intravenous administration of arbsartan, and erythromycin had no clinically significant effect after oral arbsartan administration. Fluconazole, an inhibitor of P450 2C9, decreased active metabolite concentration. The pharmacodynamic consequences of concomitant use of arbsartan and inhibitors of P450 2C9 have not been examined.
To report an adverse event, contact your Regional Adverse Reaction Monitoring Office at 1-866-234-2345 or write to: ABEE Pharmaceuticals Inc., 375 Kingston Road, Suite 200, Pickering, Ontario, L1V 1A3.

Administration

ARBACE (arbsartan sodium) may be administered with or without food; however it should be taken consistently with respect to food intake at about the same time every day.

Hypertension
The dosage of ARBACE must be individualized. Initiation of therapy requires consideration of recent anti hypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with ARBACE may need to be adjusted.

Monotherapy
The usual starting dose of ARBACE is 50 mg once daily.
Dosage should be adjusted according to blood pressure response. The maximal antihypertensive effect is attained 3-6 weeks after initiation of therapy. The usual dose range for ARBACE is 50 to 100 mg once daily. A dose of 100 mg daily should not be exceeded, as no additional antihypertensive effect is obtained with higher doses. In most patients taking ARBACE 50 mg once daily, the antihypertensive effect is maintained. In some patients treated once daily, the antihypertensive effect may diminish toward the end of the dosing interval.
This can be evaluated by measuring the blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dosage, or an increase in the dose should be considered. If blood pressure is not adequately controlled with ARBACE alone, a non-potassium-sparing diuretic may be administered concomitantly. For patients with volume-depletion, a starting dose of 25 mg once daily should be considered.

Concomitant Diuretic Therapy
In patients receiving diuretics, ARBACE therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of ARBACE, to reduce the likelihood of hypotension. If this is not possible because of the patient's condition, ARBACE should be administered with caution and the blood pressure monitored closely. Thereafter, the dosage should be adjusted according to the individual response of the patient.

Type 2 Diabetic Patients with Proteinuria and Hypertension
The usual starting dose is 50 mg once daily. The dose may be increased to 100 mg once daily based on blood pressure response. ARBACE may be administered with other antihypertensive agents (e.g., diuretics, calcium channel blockers, alpha- or beta-blockers, and centrally acting agents) as well as with insulin and other commonly used hypoglycemic agents (e.g., sulfonylureas, glitazones and glucosidase inhibitors).

Dosage in the Elderly
No initial dosage adjustment is necessary for most elderly patients. However, appropriate monitoring of these patients is recommended.

Renal Impairment
No initial dosage adjustment is usually necessary for patients with renal impairment, including those requiring hemodialysis. However, appropriate monitoring of these patients is recommended.

Hepatic Impairment
An initial dosage of 25 mg should be considered for patients with hepatic impairment, or a history of hepatic impairment (see PRECAUTIONS – Hepatic Impairment, and PHARMACOLOGY).

What is a PI ? continued . . .

1. Product Monograph ARBACE® (arbsartan sodium), ABEE Pharmaceuticals, 2006.
2. Chang DL, et al. for the BEAN study investigators. Effects of arbsartan sodium on renal and cardiovascular outcomes in hypertensive patients with type 2 diabetes and nephropathy. *Am J of Med.* 2000;9:60-71.

A randomized double-blind study involving 2012 patients, comparing arbasartan sodium (50 to 100 mg once daily) with placebo, both taken in addition to other anti-hypertensive treatments (calcium channel blockers, diuretics, alpha blockers, beta blockers and centrally acting agents). Mean study duration 4.1 yrs. A total of 327 patients in the arbsartan sodium group reported a doubling of the baseline serum creatinine, and end stage renal disease, versus 359 in the placebo group (risk reduction, 12%; p=0.002). Compared to placebo, arbasartan sodium reduced the incidence of doubling of creatinine clearance in 15 vs. 11.9 events per 100 patient years (risk reduction, 20%; p=0.006) and end stage renal disease in 12.1 vs. 9.4 events per 100 patient years (risk reduction 24%; p=0.002).

3. Brad ML, et al. A clinical study comparing arbsartan sodium with enalapril maleate in patients with essential hypertension. *Am J Hyper Research.* 2001;20:599-609.

A randomized double-blind parallel study with 576 patients randomized after a 4 week placebo baseline period to 8 weeks of once daily arbasartan sodium 25, 50 or 100 mg, enalapril maleate 20 mg or placebo. After 8 weeks of treatment, mean reduction from baseline in supine systolic/diastolic pressure 24 hours after dosing (trough) for arbsartan sodium 25 mg was 7.8/6.8mm Hg, for 50 mg was 15/12.1mm Hg, for 100 mg was 8.9/9.9mm Hg, for enalapril maleate 20 mg 16.7/13.3 mm Hg, and for placebo was 5.8/7.6mm Hg. Compared with mean changes in supine diastolic pressure in the placebo group, arbsartan sodium 50 to 100 mg and enalapril maleate 20 mg produced statistically significant reduction (p<0.001) in blood pressure. At 24 hours after doing, blood pressure changes obtained with arbsartan sodium 50 mg were similar to those with enalapril maleate 20 mg (p=0.11).

Supplemental Product Information

ADVERSE REACTIONS

In double-blind controlled clinical trials, the following adverse reactions reported with ARBACE occurred in ≥3% of patients, regardless of drug relationship:

	ARBACE (n=3295)	Placebo (n=1202)
Body as a Whole		
Asthenia/fatigue	3.8	3.9
Edema/swelling	1.7	1.9
Abdominal pain	1.7	1.7
Chest pain	1.1	2.6
Cardiovascular		
Palpitation	1.0	0.4
Tachycardia	1.0	1.7
Digestive		
Diarrhea	1.9	1.9
Dyspepsia	1.1	1.5
Nausea	1.8	2.8
Musculoskeletal		
Back pain	1.6	1.1
Muscle cramps	1.0	1.1
Nervous/Psychiatric		
Dizziness	4.1	2.4
Headache	14.1	17.2
Insomnia	1.1	0.7
Respiratory		
Cough	3.1	2.6
Nasal congestion	1.3	1.1
Pharyngitis	1.5	2.6
Sinus disorder	1.0	1.3
Upper respiratory infection	6.5	5.6

In these controlled clinical trials for essential hypertension, dizziness was the only adverse experience, occurring in more than 1% of cases, that was reported as drug-related, and that occurred at a greater incidence in arbsartan-treated (2.4%) than placebo-treated (1.3%) patients. In double-blind, controlled clinical trials for essential hypertension, the following adverse reactions were reported with ARBACE at an occurrence rate of less than 1%, regardless of drug relationship: orthostatic effects, somnolence, vertigo, epistaxis, tinnitus, constipation, malaise, rash.

ARBACE was generally well tolerated in a controlled clinical trial in type 2 diabetic patients with proteinuria and hypertension. The most common drug-related side effects were asthenia/fatigue, dizziness, hypotension and hyperkalemia (see PRECAUTIONS, Hyperkalemia).

Post-Marketing Experience

Other adverse reactions reported rarely in open-label studies or postmarketing use in patients with essential hypertension, regardless of drug relationship, include anemia, hepatitis, liver function tests abnormalities, drug induced cough, asthenia, diarrhea, migraine, myalgia, pruritus, taste disorder and urticaria.

Anaphylactic reactions, angioedema (involving swelling of the larynx and glottis causing airway obstruction and/or swelling of the face, lips, and/or tongue and pharynx, requiring intubation/tracheotomy in some cases) have been reported rarely in patients treated with arbsartan; some of these patients previously experienced angioedema with ACE inhibitors. Vasculitis, including Henoch-Schoenlein purpura, has been reported rarely.

Laboratory Test Findings

In controlled clinical trials for essential hypertension, clinically important changes in standard laboratory parameters were rarely associated with administration of ARBACE.

Liver Function Tests: In double-blind hypertension trials, elevations of AST and ALT occurred in 1.1% and 1.9% of patients treated with arbsartan monotherapy and in 0.8% and 1.3% of patients treated with placebo, respectively. When AST or ALT elevations ≥2X upper limit of normal were compared, the frequency was similar to that seen in placebo.

Hyperkalemia: In controlled clinical trials for essential hypertension, hyperkalemia (serum potassium >5.3 mEq/L) occurred in 1.3% of patients treated with ARBACE. In a clinical study conducted in type 2 diabetic patients with proteinuria and hypertension, 9.8% of patients treated with ARBACE and 3.4% of patients treated with placebo developed hyperkalemia (see PRECAUTIONS, Hyperkalemia).

Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.1 percent of patients with essential hypertension treated with ARBACE alone. No patient discontinued taking ARBACE alone due to increased BUN or serum creatinine.

Hemoglobin and Hematocrit: Small decreases in hemoglobin and hematocrit (mean decreases of approximately 0.11 gram percent and 0.99 volume percent, respectively) occurred frequently in patients treated with ARBACE alone, but were rarely of clinical importance. In controlled clinical trials no patients were discontinued due to anemia. Discontinuation of arbsartan treatment due to anemia was reported with post-marketing use of arbsartan.

In clinical trials, the following were noted to occur with an incidence of <1%, regardless of drug relationship: thrombocytopenia, eosinophilia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available in regard to overdosage with ARBACE (arbsartan sodium) in humans. The most likely manifestation of overdosage would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted.

Neither arbsartan nor the active metabolite can be removed by hemodialysis.

Product Monograph available on request.

ABEE Pharmaceuticals Inc.
375 Kingston Road
Suite 200
Pickering, Ontario
L1V 1A3

Abee
ABEE Pharmaceuticals Canada
Toronto, Canada M8V 3G4

PAAB

Timeline

July 2007: PAAB Code s7 last revised

April 2009: Exploratory PI Committee formed to evaluate how current requirements are impacting PAAB clients

March 2010: Completion of qualitative research by L. Meisner & Associates Inc

April 2010: Health Canada Bilateral Meeting

- open to considering a PAAB proposal
- would want to know how fair balance will be affected

February 2011: Expert Advisory PI Committee formed

Exploratory PI Committee

Walter Rosser MD (Committee Chair)	PAAB Chair
Gloria Bowes	PAAB Vice Chair
Peter Craig	Canadian Association of Medical Publishers (CAMP)
Terry Cully	Association of Medical Advertising Agencies (AMAA)
Jim Hall	Peer Reviewed Journals
Melody Isinger	Canadian Medical Association (CMA)
Ray Chepesiuk	PAAB Commissioner
Cindy Mersky	Canada's Research-Based Pharmaceutical Companies (Rx & D)
Janet Smith	Rogers Healthcare Group

Expert Advisory Committee

Elgin Cameron (Chair)	Canada's Research-Based Pharmaceutical Companies (Rx&D)
Lynne Brunck	Canada's Research-Based Pharmaceutical Companies (Rx&D)
Dr. Nikolai Nikolov	BIOTECanada
Jim Hall	Canadian Association of Medical Publishers (CAMP)
David Elkins	Canadian Association of Medical Publishers (CAMP)
Terry Cully	Association of Medical Advertising Agencies (AMAA)
Sonal Acharya	Canadian Pharmacists Association (CPhA)
Dr. Sam Shortt	Canadian Medical Association (CMA)
Patrick Massad	PAAB Chief Review Officer

L. Meisner & Associates Inc Key Findings:

- Least preferred option: Status Quo
- Most preferred option: Replacement of PI with copy directing the reader to the Health Canada Drug Product Database
- BUT several concerns where expressed…

Concerns & Actions

- **Concern:** Uncertainty regarding extent to which Health Canada's Drug Product Database (DPD) is comprehensive and current.

- **Action:** Incorporated flexibility to link directly to the product monograph on a company controlled website.

Concerns & Actions

- **Concern:** Uncertainty about the extent to which fair balance requirements will be open to interpretation (i.e. concerns about delays due to inadvertent misinterpretations and misunderstandings).

- **Action:** The requirements are communicated clearly in the guidance document with extensive clarification and many examples. Objective boundaries were selected wherever possible to optimize predictability for the advertiser and consistency for the regulator.

Concerns & Actions

- **Concern:** Uncertainty regarding the length of the Web linkage statement and weight of fair balance

- **Action:** Provided the flexibility of multiple fixed fair balance levels. The required level of fixed fair balance would be determined by the highest claim type level included in the APS.

  Each fair balance level is pegged to objective claim types. The manufacturer could therefore anticipate the space requirements required for fair balance and select the APS claim types with available ad space in mind. For transparency and clarity, examples are included in Appendix B of the guidance document.

  Flexibility was also built into positioning as brief fair balance could be used on the face of the APS to direct the healthcare professional to another surface.

Concerns & Actions

- **Concern:** Uncertainty about fair balance ease of use for healthcare professionals.

- **Action:** Conveyed clear formatting requirements which ensure ease of use. Information can be located easily without reading the entire standard fair balance.

Main Conclusion

Communications related to this potential change need be abundantly clear.

Particularly with regards to:

- Why the change is being made
- Reassurance about ease of use for physicians,
- Accuracy of product monograph
- Exactly what needs to be in the fair balance.

This is the basis for the extent of explanation and the number of examples provided in the guidance document.

Proposed Code Change – in brief

Fair balance on the face of the APS:

- Standard fair balance
- Brief fair balance
- General statement of risk

Which conveys risks and directs the reader to one of the following a link destination for the monograph:

- Product website*
- Corporate website*
- Health Canada website

*May also contain Dear HCP letter, study parameters, and/or reference list

Standard Fair Balance Example

Most Serious Warnings and Precautions

Pregnancy: Can cause injury or even death of the developing fetus. When pregnancy is detected, COZAAR should be discontinued as soon as possible.

Other Relevant Warnings and Precautions

- hypotension
- decreased coronary perfusion
- dosing reductions in patients with hepatic impairment or a history of hepatic impairment
- renal impairment
- hyperkalemia
- anaphylactic reactions and angiodema.

For More Information:

Please consult the product monograph at www.cozaarPM.ca for important information relating to adverse reactions, drug interactions, and dosing information which have not been discussed in this piece.

The product monograph is also available through our medical department. Please call us at 1-800-XXX-XXXX

Brief Fair Balance Example

Consult the complete product monograph at www.cozaarPM.ca for important information about:

- the most serious warning and precaution regarding risk of injury or death to fetus
- other relevant warnings and precautions regarding hypotension, decreased coronary perfusion, renal impairment, hyperkalemia, anaphylactic reactions and angiodema.
- adverse reactions, drug interactions and dosing instructions

The product monograph is also available through our medical department. Please call us at 1-800-XXX-XXXX

General Statement of Risk Example

Consult the product monograph at www.cozaarPM.ca for contraindications, warnings and precautions, adverse reactions, drug interaction, and dosing instructions. The Product monograph is also available through our medical department. Please call us at 1-800-XXX-XXXX

Note: This replaces “HCP reminder ads” (currently s7.4)

Highest Level of Messaging in the Piece		Required Level of Fixed Fair Balance
Are there one or more: • therapeutic claims, • claims relating to place in therapy, • tolerability, • compliance/adherence, • beneficial aspects of risk/burden profile from TMA* or • pharmacoeconomic benefit?	YES	Standard fair balance
No Are there one or more: • pharmacologic claims other than any of those listed above (e.g. pharmacokinetic/pharmacodynamic), • presentations describing predefined measured endpoints from clinical trials without disclosing results (e.g. ongoing studies)?	YES	Brief fair balance
No Are there one or more: • Non-pharmacologic claims (i.e. no pharmacologic claim other than the indication). See section 3.5.1 of this document. • Product messages which are not marketing benefit claims (aside from indication) or • Messages which are not about the product?	YES	General statement of risk
No There are no messages other than drug name +/- claims listed in PAAB code s6.6. APS is exempt.	YES	None

Evidence

Evidence

- PAAB commissioned research:
  - Conducted by Don Husereau
  - literature search and consultation with world thought leaders in this area
  - Full report on PAAB website

- The goal: to discover what is the state of the art thinking on the subject of evidence basis for claims in advertising.

PAAB formed a panel of experts in this area and asked them to review Don's recommendations and then vote on each of them.

Evidence Committee

- Dr. Alan Low, UBC
- Dr. Philippe Rault, Sanofi
- Dr. Philip Schwab, Abbott
- John Wong, Ogilvy Healthworld
- Don Husereau,
- Dr. Mo Amin, Amgen
- Jocelyn Marquis, Consultant
- Patrick Massad, PAAB
- Ray Chepesiuk, PAAB, committee chair

Proposed Code Change – in brief

1. Discourage p-values
2. Encourage CI
3. Update s4.1
4. Consider Bayesian statistical testing
5. Discourage use of trials which were not registered
6. Qualitative results from a systematic review should be made available if claims from individual studies are used
7. Discourage use of meta-analysis

Proposed Code Change – in brief

8. Consider use of unpublished research findings
9. Consider use of subgroup analysis
10. Consider claims from secondary outcomes
11. Discourage post hoc analysis
12. Consider claims from observational studies
13. Consider claims based on mathematical modeling

Proposed Code Change – in brief

14. Discourage use of network meta-analysis
15. Consider comparative effectiveness claims from non-inferiority trials
16. Consider claims based on economic evaluation
17. Consider claims based on HRQoL and PRO measures

Additional Proposal

Inclusion of:

"This product has not shown an effect on clinical outcomes"

In all advertisements for products whose Health Canada approval is based only on surrogate endpoints.

PAAB Commissioner comment: The PAAB Executive committee would prefer to see more precise wording reflecting individual products and what is stated in the product monograph. Ideally, Health Canada would address this issue during Product Monograph review.

Online activities s6.5

Process

- In 2011, the PAAB commissioned on online activities conducted by Canadian pharmaceutical companies.
  - Dr. Michael Law

The PAAB struck an expert committee to review section 6.5 of the PAAB Code with a view to modernizing the requirements in light of the recommendations in the report.

The committee has put forward the proposed draft for s6.5 of the PAAB Code for stakeholder comment.

Online Committee Members

- Ray Chepesiuk (Chair)
- Joanne Skedelsky, Pfizer
- Deirdre Cozier, Sanofi
- Christian Otte, Amgen
- Alex France, Brightworks
- Brad Einarsen, Klick
- Fiona Birch, Tonic Global
- Tim Dunn, Lawyer
- Patrick Massad, PAAB

Highlights

s6.5.1	Scope of code section
s6.5.2	Disclosure of company name
s6.5.3	Elements which undergo preclearance
s6.5.4	Links
s6.5.5	Banner & pop-up ads
s6.5.6	Access control (i.e. gating)

Highlights (Continued)

s6.5.7	Privacy
s6.5.8	Static online content
s6.5.9	Dynamic online content
s6.5.10	Search Engine Optimization
s6.5.11	Search Engine Marketing

The code section also includes definitions.

Supplementary guidelines will be created to support the code change.

Nonprescription and Natural Health Product Advertising Requirements

Members of the Consumer Health Products of Canada (CHPC) met with the PAAB commissioner to discuss proposed changes.

This resulted in a CHPC request for 2 changes to the code relating to nonprescription products.

Their report is on the PAAB web-site.

More Info

All documents on website

www.paab.ca

See “PAAB Code Review 2012” in the navigation bar item “PAAB Code + Advisories”

Need More Guidance ?

Webinar dates

- PI: March 6, 2012 (11:00-12:00)
- Evidence: March 7, 2012 (11:00-12:00)
- Online activities: March 8, 2012 (11:00-12:00)

Purpose:

To answer questions

Directions:

http://paab.ca/en/what_is_new/paab_code_review_201/

Contact:

Marla Weingarten, Pangaea Group Consultant

Tel: 416-516-3524

email: mweingarten@pangaea-consultants.com

Key Points

- PAAB is not creating CME guidelines
  - We are providing guidance (per industry's request) on how to interpret the Health Canada "Distinction" document and section 6.6 of the existing PAAB Code
  - Industry still has an opportunity to provide input (e.g. on format, clarity, scope)

- PAAB is working on a code revision relating to PI & Fair balance, evidence, online activities, and nonprescrition healthcare products.
  - Have your say

- PAAB is here to help you

Thank You

patrickm@paab.ca