Post-NOC Changes: Safety & Efficacy

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Overview of S&E Presentation

Discussion of :

- the new criteria for categorizing submissions;
- the new recommendations re supporting documentation




New Criteria for Categorization

-Revised criteria by which to categorize changes to PM / label:

i.e. now explicitly and consistently based on risk-management principles

-In contrast to old criteria (ie from 1994 policy), which effectively divided SNDSs from NCs based on which PM sections were being revised




Problems with 1994 “NC” Policy

- The driver behind this policy was to reduce the # of SNDS, which contributed to tendency to consider NCs as of “lesser importance”, and requiring lesser work by reviewers .....

….which was reinforced by the shorter time-line




Previous Categorization

Change to Marketed New Drug Products (1994) **ie “Notifiable Changes”**

NC = change in overdose, side effects, contraindications, warnings and precautions, where no direct or indirect claim is made

SNDS = change in dosage form or strength, route of administration, dosing, or claims, including indications.




Problems with 1994 “NC” Policy

- NCs tended to be seen as of lesser importance

- Classification primarily by PM section resulted in inconsistencies

  eg a safety update became an SNDS if revision included warning text in Dosage & Admin




Revised Criteria:

Shorter review Timeframe = Changes that are about **improving risk management** e.g. identifying, characterizing risk; adding / revising Warnings or other instructions recommendations (ie “Conditions of Use”)

= Level II (90 days)

Longer review Timeframe = Changes with the potential to **increase exposure (population or individual)** e.g. new indications, new route of admin, safety claims, new dose

= Level 1 (SNDS) *




Revision to Categories

? Sponsor asked: What about those PM changes which fit neither of the two categories?

ie changes which simply add information, neither

a) managing risk (ie therefore in some way altering existing “conditions of use” text), nor

b) potential to increase exposure, via claims etc

eg (some) changes to DRUG INTERACTIONS, or pre-clinical data, or OVERDOSE etc




Revision to Categories

Re Changes which can be argued to fit neither

-RISK MANAGEMENT nor

-NEW CLAIM / MORE EXPOSURE,

……but for which oversight is still required

Solution: Middling timeframe of 120 days was suggested, as a sub-set of Level II




Revised Criteria:

Thus, now three Categories

Longer review Timeframe = Changes with the potential to **increase exposure** (e.g. new indication, safety claims, new dose) = **Level I Supplement 300 days***

Shorter review Timeframe = Changes that are about **managing risk** (identifying, characterising, making recommendations etc.) **= Level II (90 days)**

Middling Timeframe = Changes requiring oversight, but which fit neither of the above = **Level II (120 days)**




Revision to Categories

- **<u>Elimination</u> of Level IV** (ie non-oversight changes) for S&E

  (ie Level IV now retained as a category for **Quality** changes only)




Totality of New Categories

Oversight required prior to implementation:

- **Level I (300 days & 180 days)** Benefits/ Claims / Increase in exposure
- **Level II (90 days)** Managing Risk
- **Level II (120 days)** Catch-all for remainder

Oversight **not** required prior to implementation:

Level III - Annual Notification




Level I Supplements: Examples

-**a new indication has been added** (for VDD: addition of new species) or revision to INDICATION other than for risk management;

-**change to text anywhere in PM referring to potential benefits/claims of the drug,** whether efficacy or side-effects, such as:

-PM revisions related to studies of specific sub-populations exposed to recommended therapeutic dosing (eg Special Pops);

-changes to Mechanism of Action of the drug; change to CLINICAL TRIALs which results in a new claim.

-**any diminishment to cautionary/risk management text** anywhere in the PM




Level II (90 days): Risk Management

Examples:

-new CONTRAINDICATION, WARNING, PRECAUTION, or clarifying / strengthening existing text;

-identifying / characterising adverse event, or recommendations in managing the risk;

-alteration to conditions of use, for risk management

-risk management concerns resulting from a drug interaction study;

-new overdose symptoms / treatment added;




Level II (120 Days) Changes

Oversight required, but changes do not alter conditions of use / affect advertising

Examples:

- changes to OVERDOSE other than symptoms/treatment;
- addition /change to DRUG INTERACTION that is not considered to alter conditions of use / risk management ie no precautionary wording, but also insufficient for a claim, because not therapeutic dose / duration)
- changes made to the Pharmacokinetics section in ACTION AND CLINICAL PHARMACOLOGY that do not alter conditions of use, or imply benefit/claim;
- REFERENCES: addition that does not expand claims.




Elimination of “default” date

Replaced the 90 day **default** date (as NCs), with 90 day **target** date, for Level II (90 day) changes

Since Level II (90 day) changes are about managing risk, that means: If review cannot be completed in the target time, a judgement call is required as to whether interim PM changes are needed ie until the review can be completed.




Re Supporting Information

- Part of the intent is to minimize time spent by HC reviewers requesting, and waiting for, information that provides essential context

- The more complete the initial submission, the fewer delays, as the entire picture is needed for optimal regulatory decision-making.




Re Supporting Information

"Contextual Para" on Documentation:

"Regulatory decision-making is optimal when contextualized via a variety of information beyond the data itself…"

- This "contextual information" is not a requirement for screening; rather, it is anticipated that **the sponsor will not be silent on the issue**

ie EITHER provide the information, OR acknowledge the absence, and why

-Case-by-case judgement call by review staff as to whether an absence is a problem in an individual file




Re Supporting Information

Common to Level I (Supp.) and Level II (NC) includes:

- clinical and /or non clinical study data e.g. efficacy, PK, PD, epidemiological, pharmacovigilence, studies in PSURs
- data other than from study reports: e.g. PSURs, review /reports / analysis of safety concerns; publication-only studies; real-world drug use information; abstracts;
- copy of most recent core data safety sheet;
- copies of most recent labelling from other major ICH jurisdictions;
- copes of pertinent communications with these agencies.
- other relevant info: e.g. sponsor rationales; RMPs; expert opinions; reviews; advisory transcripts;




Re Supporting Information

Specific to Level I (300 days, 180 days)

- where available, copies of any relevant foreign review reports, Q & A etc from other major ICH jurisdictions
- summary of substantive issues raised by other jurisdictions and how they were resolved (or statement that there were none)

Specific to Level II (90 days)

-any communications to health professionals/patients (OR explicit statement confirming lack)

- Most recent PSURs (cumulative & non-cumulative) if the risk issue in question is addressed in the PSUR




Thank You

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QUESTIONS

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