Creation of Justification Documents to support CDS changes

One of the 'ongoing issues' handed over to the Labelling Experts from the GPI directors was how to resolve the problem of creating Justification Documents post SERM that are 'fit for regulatory purpose' but at the same time meet the legal requirements that are now mandatory within our company. This has been an issue for more than 18 months and has led to AstraZeneca being out of compliance with its internal SOP timelines (SOP-332-G section 2.4) [1,2] - which was highlighted in audit report 04SYS001dated 23 November 2004 [3].

Background

Originally, JDs were created by Drug Safety with the sole purpose of providing a justification for making safety changes to the company Core Data Sheet post SERM, which could then be sent to the Marketing Company for submission to the local Regulatory Authority in support of consequential changes to the Market Data Sheet.

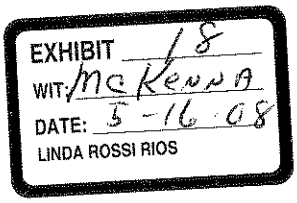
In recent years the external environment has changed, such that there is now a perceived medico-legal need to have an internal AZ document, to formalise the completion of the actions agreed to in SERM. Thus, a single document now has to serve a dual purpose, that of 'internal medico-legal finalisation of SERM' and 'external regulatory document'. Resolution of these differing (sometimes conflicting) needs has resulted in extended and sometimes multiple document reviews of the JDs, which in turn has significantly delayed finalisation and sign-off of the JDs and amended Core Prescribing Information and subsequent dispatch of these documents to the markets. Thus we now have an unacceptable situation where the company is out of compliance, together with a laborious and frustrating work situation for the people handling the JDs.

Unsurprisingly, a report dated 16th July 2004 [3] which followed an internal audit of the processes for updating the company Core Data Sheets, included the finding that AstraZeneca often did not meet its own internal SOP timelines for sign-off of the updated texts and dispatch of the amended documents to the markets.

Customer requirements

We have received feedback (both formerly in GPI and in our current Labelling Expert role) from some of the markets that the Justification Documents that we are currently supplying them with are no longer 'fit for regulatory purpose'. This is partly because they are perceived to be too long (containing additional text that has been added on the advice of Legal and which is perceived by the MCs as being superfluous or irrelevant to the issue, hence inappropriate for submission to the authorities). Consequently, it is believed that some MCs may be re-writing the JDs and submitting the amended documents to their authorities – indeed the US are already doing this.

Additionally, it has been highlighted by the EU group that as of 1st May 2005, the current JD format is not CTD compliant, ie it does not follow the mandatory format and headings as presented in the Notice to Applicants- either as a Clinical Overview (module 2.5) or a Safety Summary (module 2.7.4) - (see link:



http://pharmacos.eudra.org/F2/eudralex/vol-2/B/ctd_06-2004.pdf). This means that the marketing company either has to convert the JDs so that they appear as a Clinical Overview (and then refer to the local prescribing information) or the JD could be left as it is, but the MC would then have to add a step to reshape the approved into a proper Variation Application, in the proper format which is then fit for filing with the authorities.

Finally, prior to the AZRA reorganisation, the ICOS group were tasked with the responsibility of creating 'Abbreviated JDs' using a template which allowed for a relatively simple administrative exercise to create a shortened version of the main, signed-off JD, which was then suitable for submission in some International and former MSDO markets.

The JD template and abbreviated JD template were designed to allow a straightforward 'mapping' of the required sections from the signed-off JD into an abbreviated JD. As ICOS no longer exists, but International still require an abbreviated JD for their markets, there is currently an unresolved issue in satisfying the needs of these markets.

Possible Solutions

1. Drug Safety could create a Justification Document which is 'fit for regulatory purpose', ie which the MCs could submit direct to their authorities without the need for any further editing. If an agreement on the JD template format could be reached between Drug Safety and Regulatory and the resulting template were followed, there should not be any need for extended or repeated review cycles to agree the content, therefore it should in most cases be possible to meet the SOP timelines. If the template were sufficiently brief, International would be also able to use this document without further editing.

   If there is a need for a second, 'internal', medico-legal JD, this could be created separately and off the critical path. It could probably be created from the Discussion Document (which already would have had Legal signoff before SERM) without too much editing, provided that the Discussion Document template and this template are aligned, and together with the SERM minutes, should be sufficient to provide the company with a 'finalisation of SERM actions'.

   A decision would have to be made by the business regarding the format of the 'regulatory JD', ie whether or not to use the CTD Clinical Overview headings. There are several reasons against doing this. It is actually quite difficult in practice to use the standard CTD format headings for a justification for a CDS update, as they refer to topics more usually discussed in a new or line extension application, eg "Product Development Rationale" etc, therefore it would require more Drug Safety (or Regulatory) resource to write the JDs in this format. Moreover, providing the JDs as a Clinical Overview would be quite novel to many markets, and therefore the possibility exists that they might create and submit a new JD in the 'old' format.

2. Drug Safety could create their 'Medico-Legal JD' using a template whose format was agreed between themselves, Legal and Regulatory. A separate 'regulatory JD' could then be derived from the first JD by 'mapping' sections from one template to the other.

   We have attempted to create a 'regulatory JD template' from the existing JD template, however in practice (and as discussed above) this is difficult to do, especially as the text from the JD is having to be 'squeezed' into the CTD paragraph headings. The resulting JD ends up being not much shorter (or more regulatory-focussed) than the original. Another disadvantage of deriving the 'regulatory JD' from the 'medico-legal' one is that either both documents would have to be created and reviewed in parallel, or alternatively, the regulatory document would have to be created ***after*** the medico-legal one was signed off, which would increase the timelines for dispatch of the variation to the markets, a situation we would clearly wish to avoid. [4,5]

3. We could accept the 'status quo', and allow longer timelines for creation, review and finalisation of the JDs, also accepting that there may be conflict between of the two purposes of the document, which in turn would lead to continuation of the contentious and extended review cycles. If we do this, we would recommend extending the SOP timelines to avoid the issue of non-compliance.

Conclusion

We believe that Drug Safety should be providing us with a document that is 'fit for purpose' ie is brief, focussed and does not introduce any new topics or information that would give rise to questions from the regulatory authorities and thus delay approval of safety changes in Market Data Sheets. If they have an internal requirement for a separate medico-legal document, this should be created separately and off the critical path, and should not require review by Regulatory (as is currently the case for Safety Position Papers). We would also recommend that this document is sufficiently brief that it can be used by International without any further editing.

Our view is that if the MCs are able to submit Justification Documents using an in-house, non-CTD format which could be submitted under an indent in the CTD variations template, this would be preferable to using the CTD Clinical Overview format, which does not readily lend itself to the creation of an justification for a change to a Market Data Sheet.

From the perspective of the Labelling Experts, it is absolutely imperative that this business process is sorted out as soon as possible, as updating of the GRP 3.3 (and subsequent training of Global RADs and RAMs on this GRP) is dependant on it. It is also essential that the business has processes which allow compliance with its own internal SOP.

We would welcome the opportunity to discuss this with you as soon as possible.

References

1

SOP-332-G
3rd June KA.do

2

getDocument.url

3

04SYS001
ty Signal Gener

4,5

Draft jd 10 Feb 05.doc

DRAFT JLATORY JD v 3