The Benefits of Joining nCADREAC

Andrea Herrmann and *Harald Schweim* explain why the initiative that helps would-be EU member states get used to stricter drug regulation is still worth joining.

One might think that CADREAC, the Collaboration Agreement of Drug Regulatory Authorities in European Union Associated Countries that was launched in 1997 to help countries that were due to join the EU meet the strict regulatory standards laid down in EU drug legislation, has outlived its usefulness given that all except one of the original signatories are now full members of the union.

However, new members have joined the initiative and, in May 2005[1], the original agreement was replaced by the "new CADREAC" or "nCADREAC".

nCADREAC replaced the original agreement in 2005 and new members have joined the initiative

This article examines the history, present and future of CADREAC/nCADREAC. It argues that there are indeed reasons for other countries that might be potential EU member states, such as those in south east Europe to join the initiative. Member countries can offer the nCADREAC procedures as alternatives to their national procedures and harmonise their regulation of medicinal products so that they comply with high scientific standards laid down in EU legislation.

Background

Bulgaria, Cyprus, the Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Slovakia, Slovenia and Turkey all signed the original CADREAC agreement. With the exception of Turkey, whose accession date has not yet been confirmed, they have all since joined the EU.

It would seem logical that the CADREAC procedure would have ceased to exist in 2007, ie the accession date of the last two countries – Romania and Bulgaria – to join the EU. Instead, new countries became members of CADREAC. Of the former observers of CADREAC – Belarus, Bosnia-Herzegovina, Croatia, the Republic of Moldova, Macedonia, Montenegro, Serbia, Switzerland and Ukraine – only Croatia is a member of nCADREAC and applies CADREAC/nCADREAC procedures.

Mission, function and responsibilities

The mission of the original CADREAC was to facilitate the transition of regulatory conditions in EU associated countries to achieve regulatory standards required by the *Acquis Communautaire* – ie the body of EU legislation (notably, in this case, compliance with Article 6 of Directive 2001/83/EC[2] on human medicines as amended by Directive 2004/27/EC[3]). It called for the implementation of EU regulatory standards; the involvement in professional activities within the EU; the introduction of mutual recognition procedures; the introduction of centralised procedures; the development of common strategies; the preparation of meetings; and information exchange.

The mission of the original CADREAC was to facilitate transition of regulatory standards in EU-associated countries

CADREAC procedures and agreed documents include the following:

- common procedure on the granting of marketing authorisations by CADREAC drug regulatory authorities for medicinal products authorised in the EU under the centralised procedure;
- common procedure on the granting of marketing authorisations by CADREAC drug regulatory authorities for medicinal products authorised in the EU under the mutual recognition procedure. A revision of the guideline – published on 10 June 2001 – includes the retrospective inclusion of medicinal products for human use authorised in the EU via the decentralised procedure (essentially identical to the MRP) in the common CADREAC simplified system[4];
- common CADREAC procedure for retrospective inclusion of centrally authorised medicinal products for human use in the common CADREAC simplified system;
- standard operating procedures;
- lists of contact points; and
- lists of CADREAC observers in EU/European Medicines Agency working parties and of observers to CADREAC.

CADREAC Standard Operating Procedure-3 was adopted in April 2001, defining the responsibilities and function of a CADREAC secretariat[5]. From 1997-2004 the collaboration had a yearly rotating presidency that also hosted the secretariat, but since March 2004, the secretariat has been located at Romania's National Medicines Agency.

The CADREAC secretariat is based at the Romanian National Medicines Agency

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nCADREAC's procedures, which were released on 10 January 2006, are nearly identical to those of the original CADREAC[6,7]. The active members of nCADREAC are Bulgaria, Croatia, Czech Republic, Hungary, Romania and Slovakia. Kosovo and the Republic of Moldova are collaborative members[8]. (Based on the CADREAC rules, it is mandatory to have at least six countries in the collaboration to be able to recruit new CADREAC countries and to keep CADREAC alive. Therefore, some EU member states are still members of CADREAC.)

Croatia is currently the only country that can use nCADREAC procedures

Until 2007, it was possible for Bulgaria, Croatia and Romania to use the nCADREAC procedures for products authorised via the centralised, decentralised and mutual recognition procedures. But now that Bulgaria and Romania are EU member states, Croatia is the only country that can use nCADREAC procedures.

It is logical that other south eastern European countries that might be potential EU member states (such as Macedonia, Kosovo, Turkey, Moldova, Serbia, Montenegro or Bosnia-Herzegovina) should become members of nCADREAC. Most of these countries have already implemented many EU regulations and guidelines, but, so far, there are no alternative procedures in place except national procedures. These national procedures are often lengthy (eg review of a marketing authorisation application can take two to three years in Turkey or 12-15 months in Macedonia) and national regulations and guidelines are often not 100% harmonised with the EU. This can make marketing authorisation application procedures rather difficult in these countries.

Some countries also implement additional regulations in addition to EU regulations that can cause difficulties for marketing authorisation application sponsors. For example, in Turkey a new law on good manufacturing practice came into force on 1 March 2010. Under this law, the Turkish authorities no longer accept GMP certificates from other countries and must carry out inspections of manufacturers that submit a marketing authorisation application after 1 March 2010 during the ongoing evaluation procedure. Such inspections can take time and lead to delays in approval.

Also, it takes time for different EU countries to implement new EU regulations nationally into their laws. It can be difficult for marketing authorisation applicants and authorities to deal with the situation where countries have not yet implemented EU regulations. The nCADREAC initiative, on the other hand, can be implemented quite soon after the implementation of a new EU regulation. This would, at least, facilitate the implementation of the regulation into national law in the different countries.

Products authorised via nCADREAC procedures are already in line with current EU legislation

nCADREAC makes a potential EU member state accession easier, as the products authorised via nCADREAC procedures are already in line with current EU legislation. Based on all these arguments, it is advisable that such countries become members of nCADREAC and also establish the nCADREAC procedures in their national law.

Different CADREAC/nCADREAC procedures

The CADREAC and nCADREAC procedures for products authorised in the EU via the centralised procedure or the mutual recognition procedure provide member countries with a simplified procedure of registering a medicinal product in their country.

The basis for the assessment for the CADREAC/nCADREAC drug regulatory authority is the original dossier that was submitted to and approved in the EU for the mutual recognition procedure (by the reference member state and concerned member states) or for the centralised procedure (by the European Commission).

The national procedures in the different CADREAC/nCADREAC countries are completely independent and involve the submission of country-specific dossiers. The evaluation of the dossier is undertaken independently by the national authority of each country.

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CADREAC and nCADREAC procedures offer the possibility of harmonising SmPCs and PILs

For example, they offer the possibility of harmonisation of labelling texts (summary of product characteristics (SmPCs) and patient information leaflet (PILs)) and the documentation of medicinal products authorised in EU member states via the mutual recognition procedure or centralised procedure with the CADREAC and nCADREAC member states; this is due to the fact that the documentation and labelling documents that have to be submitted in EU member states and in CADREAC and nCADREAC countries are identical. This also has advantages in terms of life-cycle management, in that the handling of any changes and variations can be executed very simply.

On the other hand, while this harmonisation of labelling documents is a prerequisite for generics, it is in fact carried out by the originators. Thus, generics companies can apply for and get easier marketing authorisations, and enter the market earlier and more easily; this is a clear advantage for generics but a big disadvantage for originators. If a product is authorised via the national procedure in each nCADREAC country, the SmPCs and PILs may not be harmonised. In such cases, the way for generics to get marketing authorisations is more complicated due to the fact that the generics companies themselves have to fulfil the requirement for generics (ie they have to harmonise the SmPCs and PILs themselves; it is not done by the originators). Therefore, the nCADREAC procedure has a clear advantage for generics companies.

Another advantage of the simplified nCADREAC procedure is the potential for time saving. nCADREAC procedures take less time than national procedures for gaining marketing authorisation. The nCADREAC procedure for products authorised in the EU via the mutual recognition procedure takes between four and 12 months depending on the review time in each country: the shortest review time is in Bulgaria, at 120 days, Romania takes six months (usually there is a delay of three to four months) and the longest review time is in Hungary, at 12 months. The nCADREAC procedure for products authorised in the EU via the centralised procedure takes between two and seven months, depending on the review time in each country: the shortest review time is in Estonia at two months, Romania takes three months and Turkey takes the longest time to review, at seven months.

nCADREAC procedures take less time than national procedures for gaining marketing authorisation

Conclusion

We reiterate that, given the obvious advantages of nCADREAC membership, it is advisable that other south eastern European countries that might be potential EU member states join the initiative and offer the procedures in their countries as an alternative to national procedures. This offers more options for marketing authorisation applicants, but also for authorities, as they can use EU procedures and documentation (such as assessment reports) as a basis for their evaluation. In addition, being part of nCADREAC makes it easier when it comes to preparing to align with EU regulations before joining the union.

Joining nCADREAC gives marketing authorisation applicants and authorities more options

When deciding which procedure to use for the marketing authorisation application of a product in nCADREAC countries, several aspects should be considered. These include: flexibility of the applicant/marketing authorisation holder; duration of the marketing authorisation procedure; evaluation procedure of the dossier; date for submission of a marketing authorisation application; the stage the product is at in its life-cycle; the status of harmonisation of the dossier and the labelling documents; and the costs of the procedure.

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