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A brave new Europe with the introduction of the EU Clinical Trials Directive: Impact upon the pharma industry and academic research with special emphasis on pharmacovigilance

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Abstract

1st May, 2004, saw the national implementation of the EU Clinical Trials Directive (2001/20 EEC). Additionally, Europe changed from 15 to 25 member states, all implementing the Directive nationally at the same time and all being affected by the many and varied aspects covered in the Directive. The paper looks at the new changes to European clinical trials and what this will mean for the pharmaceutical industry and research academia alike, especially in relation to safety reporting and risk/benefit assessments.

Keywords: *clinical trials, Directive, pharmacovigilance, electronic submissions, SUSARs*

INTRODUCTION

Since April 2001 when the EU Clinical Trials Directive became adopted within Europe the clock has been ticking towards national adoption, a date that was fixed in April 2001 as being 1st May, 2004. This allowed the member state countries 36 months to put the European Directive into national legislation.

The EU Clinical Trials Directive arose out of the recognition that although all 15 member states were part of a united Europe there were both subtle and sometimes dramatic differences in the requirements for the conduct of clinical trials. The hope was that the Directive would provide one way of performing clinical trials to a defined and uniform standard.

Coincidentally, the date of 1st May, 2004, also provided the politicians and regulators with another challenge, that of European expansion, the 15 member states increasing to 25 – an overnight increase of 66 per cent in membership (see Table 1). The addition of the extra member states into Europe, for the first time meant that the number of peoples within the EU exceeded the population of the USA, making the 25 member states the single most developed organisation for pharmaceuticals.

The EU Clinical Trials Directive (2001/20 EEC) encompasses many aspects of the clinical trials process. In order to facilitate the 18-page Directive, a succession of draft, final and revision guidance documents were released that provided explanatory detail on the various topics as an aid to implement the Directive requirements.

The guideline documents (see Figure 1) provided approximately another 200 pages of notation to the Directive. The guidance notes were first issued in draft format during 2002, inviting comments from industry and academia regarding the content of the document and any

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Table 1: Current member states and new members of the EU (phases I and II)

Current member states		Members of EEA*	Phase I Members (1st May, 2004)	Phase II Members (2007)
Austria	Italy	Iceland	Poland	Bulgaria
Belgium	Luxembourg	Norway	Estonia	Romania
Denmark	Netherlands	Liechtenstein	Slovenia	Croatia
Finland	Portugal		Hungary	Serbia
France	Spain		Czech Republic	
Greece	Sweden		Cyprus	
Germany	UK		Lithuania	
Ireland			Latvia	
			Slovakia	
			Malta	

* EEA = European Economic Area, countries that agree to abide by EU Pharmaceutical Regulations.

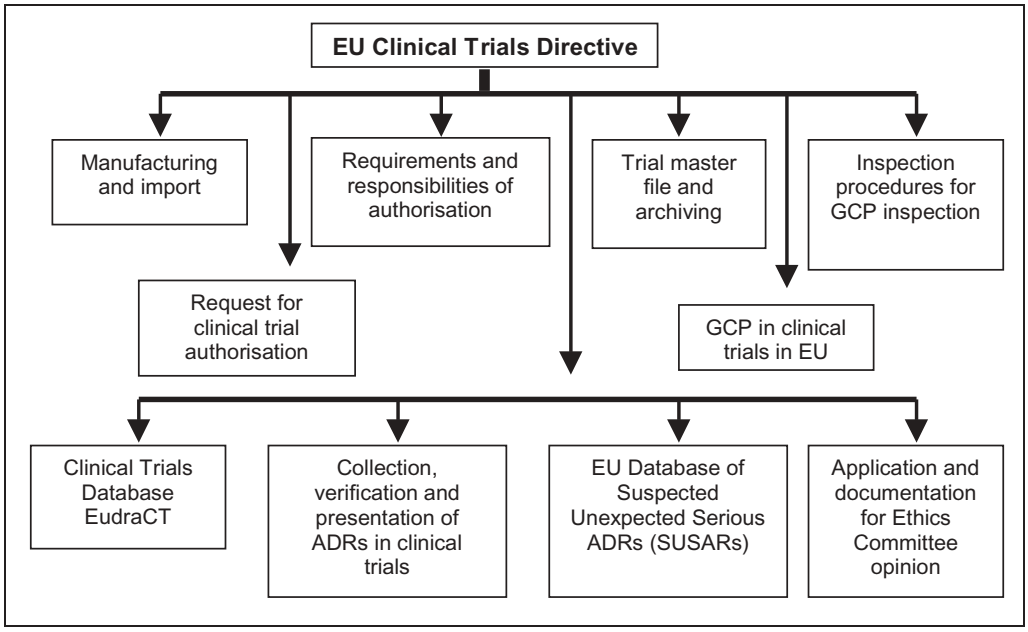

Figure 1: Guidance documents issued with the Clinical Trials Directive. ADRs, adverse drug reactions; GCP, good clinical practice

Guidance documents are required to supplement the wide areas covered by the Directive

suggestions for improvement. However, any changes had to be within the confines of the Directive, because changes to the Directive were not possible, only amendment of the guidance documents to provide greater clarity or practical application of the Directive. All of the guidance documents are available for downloading and retention from the European Agency for the Evaluation of Medicinal products (EMEA) website.

A number of the guidance documents (but not all) then proceeded (following comments) to final documentation during April 2003. These final documents were then used by industry and academia alike in order to look at and prepare for the impact the guidance notes were recommending for adoption from 1st May, 2004. Unfortunately, even the final documents of April 2003 had some features that many people from industry knew were not possible. This culminated in revisions to final documents that appeared in late April 2004, just a few days before national implementation of the Directive 2001/20 EC. The revised documents are shown in Figure 2.

The problem with late changes such as these are that companies and investigators are faced with last minute alterations and training in Standard Operating

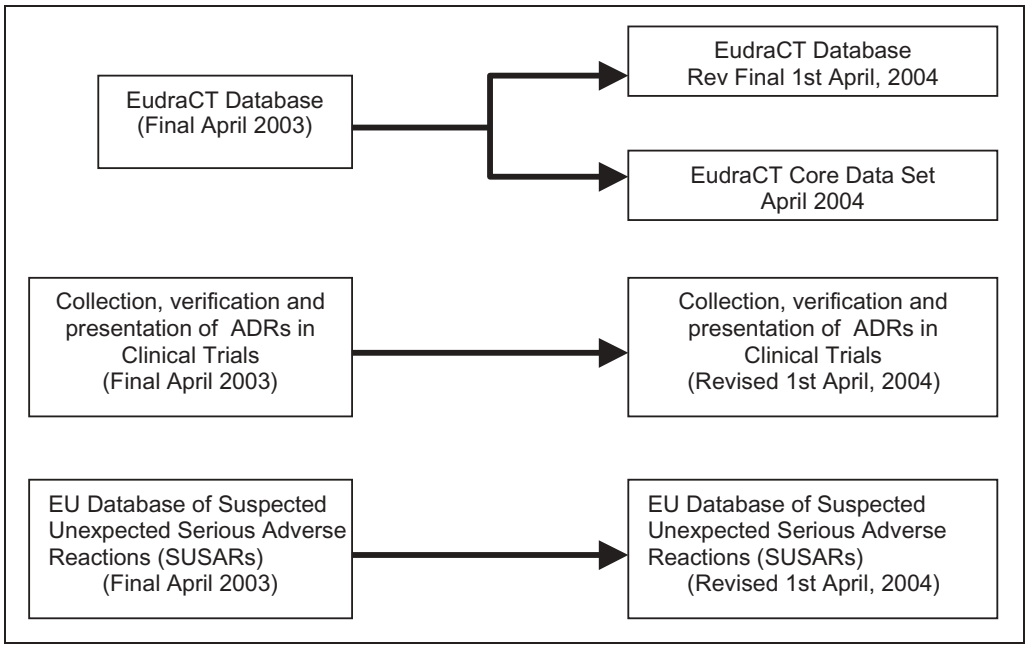

Figure 2: Final Guidance documents undergoing revision in April 2004

Procedures (SOPs) just prior to adoption of a new procedure. Each area covered by the Directive will mean changes within pharmaceutical and biotechnology companies alike, as well as for the first time, having major implications for the so called academic (investigator) lead studies.

The major implications of the Directive on patient (and volunteer) safety include a continuous safety review process looking to detect as early as possible new risks to patients and volunteers alike which could influence both the progression of the individual trial as well as the development programme. Reviews of those elements that affect the safety conduct for clinical trials in the new European environment are presented below.

PATIENT AND VOLUNTEER SAFETY – IMPLICATIONS FROM THE EU CLINICAL TRIALS DIRECTIVE

EudraCT DATABASE

Although not directly a safety issue, the approval of protocols will now be centralised in Europe and details of each protocol will appear on a single database, EudraCT. All clinical trial protocols, which proceed from the 1st May, 2004, from within the EU will require this unique number. Once the number has been applied for and generated, this number operates for the protocol throughout Europe.

The EudraCT database will contain all protocols for clinical trials

The EudraCT database captures far more than just the protocol number (approximately 200 separate data elements), also recording sponsor details, product, indication under investigation, patient population, identification of ongoing, completed or terminated trials in EU, and also any good manufacturing practice (GMP) and good clinical practice (GCP) inspection findings. The database also records any trial terminations because of safety reasons. The EudraCT database will also record all protocol amendments made to the original.

The EMEA launched the website and place for obtaining EudraCT numbers on its website on 6th May, 2004, and so all new clinical trials can have a EudraCT number.

The EudraCT database also has linkage to another proposed database under the Directive, the so-called SUSAR database (see below). Shared elements, such as EudraCT number, sponsor details and product name ensure that safety issues with a product can be linked to any

clinical trial occurring with the product throughout the whole of the EU and directly to the sponsor.

EU Database of Suspected Unexpected Serious Adverse Reactions (SUSARs)

SUSAR reporting will soon become electronic

Another new database to be created as part of the Clinical Trials Directive is the SUSAR database, an electronic individual case capture mechanism which will record all Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring for any product in clinical development within the EU. Any clinical trials occurring outside of the EU where the product is also being developed in the EU will also have to report SUSARs into the SUSAR database.

This database also reflects the capability being introduced at present with the EU, USA and Japan for electronic submission of post-marketing adverse drug reactions (ADRs). Europe alone is currently proposing an electronic system for reporting SUSARs in this way. The data elements required for the submission of the SUSAR cases are yet to be finalised but will adopt many of the elements currently expressed for post-marketing data capture. Indeed the current proposal in the EU is that the clinical trials ADR database (SUSAR database) will be able to link with the post-marketing safety database (Eudravigilance), which will aid in signal detection analyses.

This is the key purpose for this type of database – 'to slice and dice' case reports looking for signals using other data from post-marketing sources to increase the data for review and look at possible class-related effects from products with similar pharmaceutical structure.

Additionally, since Europe also had multiple collection methods and timelines for the submission of clinical trial ADRs and the types of events, the database will aid in unifying all of these processes such that there will be set data elements for the ADR reports, common timelines for ADR submission, the seven and 15 day timelines adopted by International Conference on Harmonisation (ICH) E2A for fatal/life-threatening and serious adverse reactions respectively, and the submission of SUSARs only.

There is some confusion in exactly how this will provide good signal detection processes as many pharmacovigilance people will attest to the fact that it is only by examining all cases (those reported as related as well as those currently regarded as not related) that can help detect potential signals. Additionally, since patient exposure in clinical trials may be low, only the gross common ADR signals would be the ones that would be detected in clinical programmes. However, the capability of regulators to compare classes of compounds does provide advantages over pharmaceutical companies in their safety review processes.

Access to the SUSAR database will be granted to sponsors (for their own investigational medicinal products (IMPs) only) so that sponsors can verify that all submissions made electronically are in fact stored in the SUSAR database. Submission of reports will again be via the E2B gateway mechanism that was proposed and is now in progress for post-marketed submission of ADRs.

All member states will have access to the SUSAR database and will be able to perform their own signal detection analyses. It is possible for a representative from a concerned member state (ie where a trial is taking place) to raise any concerns with the sponsor. This may result in many different questions from various authorities as they all conduct their own analysis of the data and could result in additional work for the sponsor in answering multiple authority requests. It would be useful in these circumstances if one member state took the lead in this and was the only contact with the sponsor company (including any questions from annual safety submissions) coordinating activities of other authorities almost like a 'pre-rapporteur' for safety issues for IMPs.

The SUSAR database also has links to the EudraCT database. When submitting a SUSAR report electronically, one of the data elements that need to be provided is the EudraCT number. Without the EudraCT number the SUSAR report cannot be made. This link allows the regulatory authorities to track SUSAR reports against specific protocols throughout Europe.

The electronic process for the submission of SUSARs will require an information technology (IT) infrastructure to be built by both the pharmaceutical and biotechnology industry and the regulatory agencies for sending, receipt and acknowledgment of receipt of such information across secure data highways using encrypted defined data formats. All of these processes will require testing prior to live implementation and SOPs for how these actions are performed.

The requirements for ADR reporting are now more similar to ICH and FDA reporting

The mechanism for reporting of SUSARs direct from the sponsor (or their representative) to the authority can be via an E2B gateway as happens for post-marketing safety. Unlike the post-marketing situation the EMEA has stated that it does not require retrospective submission of any historical cases for any IMP prior to 1st May, 2004.

There is a possibility of using a secure, web-based submission module which is provided free by the EMEA and which would allow for direct entry over the web (via a password protection) of any SUSAR reports. This would ideally suit small enterprises (companies) or individual investigators who were conducting private research and generating few SUSAR reports because they would not have the cost of providing their own infrastructure to generate such reports.

The EMEA has provided training courses via the Drug Information Association (DIA) for electronic reporting using the web module over the summer months in 2004 in order to train and prepare everyone for the changes and mode of transmission.

COLLECTION, VERIFICATION AND PRESENTATIONS OF ADRs IN CLINICAL TRIALS

The collection, reporting and examination of (serious) adverse events and reactions are covered by the guidance notes, which help explain and expand upon the information provided in the Directive. Determinations of expectedness are also in accordance with ICH E2A.

The Directive is quite explicit in stating that the general rule for supplying individual reports are those which are suspected (a possible causality rating); unexpected (not present in an investigator brochure or the up-to-date summary of product characteristics (SmPC)); and is a serious ADR.

The guidance notes follow the same instructions that are found in ICH E2A, thus introducing consistency in Europe for the various ICH documents. Expedited reporting is required for all SUSARs occurring in any trial in the EU and also for all SUSARs occurring outside the EU when there are active trials occurring within the EU.

Additionally, reports of increased frequency of serious ADRs, significant findings from preclinical experiments (eg carcinogenicity findings), a significant hazard to the subject population such as lack of efficacy in a life-threatening condition or if the trial design itself is causing patients serious adverse events, could also warrant suspension of the trial or modification of the existing protocol, which would then require formal resubmission using the unique protocol EudraCT number to track the changes. These reports, however, cannot be submitted electronically and must be submitted in paper format, citing the protocol and EudraCT number on any submission.

All trials in the EU must now produce annual safety report submissions, something that was not a requirement throughout the whole of Europe previously and certainly not according to

one format. The content of the line-listings together with the requirements for submitting summary tabulations of all new ADRs (expected and unexpected) throughout the anniversary of the trial are clear. These must be submitted within 60 days of the annual anniversary and must include an overall safety summary on the IMP together with a risk assessment to patients (either as a treatment population or identifying possible at risk subpopulations) and a recommendation concerning the continuance of the trial or programme based upon present knowledge and a benefit/risk assessment.

In order to prevent multiple submissions of annual reports (according to when the study began), a European birth date is given as being the date the first trial in Europe began and then every subsequent trial in a member state adopts this timeline for the annual submission so that one submission report only is required for all trials being conducted in member states. This allows such submissions to follow the same pattern as evidenced for the post-marketing periodic safety update reports (PSURs).

Independent Data Monitoring Boards are a new concept for clinical trial monitoring in the EU

Another additional introduction with the Directive is the use and setting up of Independent Data Monitoring Boards (IDMBs). The recommendation is that these groups (all members of whom are totally independent of the company) actively review the safety, efficacy and protocol designs and IMP programme and advise the company of any findings they make. The guidance notes suggest that the IDMBs should be instituted when companies are developing programmes involving development of products in life-threatening and chronic diseases where mortality and morbidity is likely to be high. IDMBs have again been recommendations in ICH initiatives (ICH E6) and the US Food and Drug Administration (FDA) has long established guidance documentation for the composition and implementation of IDMBs.

IDMBs can and will create extra work for companies that choose to have them in place (data provision, additional data following meetings, documentation of findings, follow up of advice), but since this is a Directive recommendation, the choice not to implement such a group should have a rationale as to why it would not be appropriate for the particular programme.

Findings from the IDMB are also to be made available to the regulatory authorities and so recommendations made by them to the company are expected to be followed through or to the IDMB's satisfaction. If the IDMB also recommends suspension or termination of the programme due to the findings (lack of efficacy, unacceptable safety profile) then this too needs to be followed, unless additional data can provide the IDMB with a different conclusion. IDMBs can also make recommendations to the company regarding the positive nature of the findings (better efficacy than comparator, better safety profile) and so their deliberations do not have to be negative.

Current regulations within the EU do not accommodate IDMBs and so it is little surprise that the European Committee for Proprietary Medicinal Products (CPMP) in February 2004 released a concept paper on the points to consider with IDMBs and it is anticipated that further information by way of points to consider will be developed over the next six months to aid companies when using IDMBs.

In clinical trials the use of comparator products is a requirement (where applicable) as part of the licence submission package to demonstrate efficacy and safety against a product already being used to treat the disease, syndrome, etc.

Trials are conducted against comparators and the Directive has stated that all SUSARs occurring in comparator products should also be reported by the sponsor of the trial directly to the regulatory agency and then it is possible for the sponsor to also inform the manufacturer. This places responsibility

on the sponsor to recognise an unexpected serious adverse reaction in a comparator product.

If trials are occurring multinationally, it is not unreasonable to foresee that the approved labelling for a product (the SmPC in Europe) may vary from one country to another and so the sponsor would need to know whether the observed serious ADR with the comparator product is expected in one country but unexpected in another. This will potentially create not only additional resource for the sponsor company but also a dilemma in under-reporting SUSARs for the comparator. The sponsor is also expected to inform the comparator company of the ADR but only after making its decision on reporting to the agencies or not.

Reporting ADRs in comparator products to regulatory authorities is now the responsibility of the trial sponsor

The Directive, by adopting this stance, is also not following ICH E2A guidance, which gives the sponsor company the option of either, reporting the ADR to the comparator company or the regulatory agency. It makes more sense to adopt this strategy because the comparator company can then make the determination of expectedness for its product for all the countries it is approved and decide whether to report or not, rather than a sponsor company who will not have the same in-depth knowledge of the product as the originator company.

The sponsor is also to perform an ongoing assessment of safety of the IMP and risk assessment. The implication of this is that the sponsor will be reviewing all safety reports (irrespective of causality) looking for potential safety signals and the impact of any perceived signal on the risk to the treated population or identification of an at-risk subpopulation (eg age, sex, organ impairment). This means the sponsor has to be reviewing the safety data 'in real time' as much as possible in order to make rapid assessments of potential safety problems and identify these early in order to protect the patients being treated. Since many companies utilise the services of contract research organisations (CROs) (sometimes more than one), the location and ability to review all the safety data on the IMP become crucial for signal detection and the implementation of signal detection, and risk methodology will be a focus for companies partnering with CROs in addition to central sourcing of the safety data.

Additionally, the ability to review safety data is not confined to serious events but also non-serious, since these can be warnings of more serious events waiting to happen (eg biochemical changes, blood parameter changes). Non-serious events can also influence patient compliance with a drug. A high percentage of patients experiencing nausea can greatly influence compliance and the product's success. However, much non-serious information is only routinely captured at various time points during the trial (monthly, three monthly, interim analyses) and so the influence on patient safety may be underestimated from examination of serious cases only.

The concept of risk/benefit assessments and ongoing safety surveillance during the clinical trial programme are requirements for post-marketing safety and are quoted at length in Eudralex Volume IX in European legislation.

The requirement to perform the same analysis and annual review of safety will require companies (and individual investigators alike) to use some measure to judge such benefit and risk, and by adopting the same criteria as appears in Eudralex Vol IX as well as adopting such recommendations that appear in CIOMS IV will enable companies to demonstrate due diligence in this field. Naturally, all such procedures for determination must be recorded in SOPs.

GOOD CLINICAL PRACTICE

ICH E6 has been embraced by the EU for a number of years but for the first time ICH E6 is incorporated heavily into Directive legislation, which will then be incorporated nationally and will constitute an auditable requirement both for

sponsors of trials and the regulatory authorities to ensure that GCP is being followed.

GCP inspection findings by regulatory authorities will eventually be stored on the EudraCT database

Indeed, audit findings from the regulatory inspections will be included on the EudraCT database, but this information on findings at sites, at CROs, at sponsor companies, at laboratories, etc, will not be made available to companies (except those directly involved in the audit) and so there will be no mechanism for a sponsor to know what happened regarding an audit at a site they were hoping to use in a future study. The capability of storing this information on a central database is for regulatory authorities to have knowledge on any potential problems with investigators, etc. prior to commencement of a clinical trial.

The central coordination via the EudraCT database of inspection findings will be the first time this will have been achieved. Authorities will be able to look at this data on an ongoing basis and search via sponsor companies and institutions.

ICH E6 adherence will be followed by both the pharmaceutical and biotechnology industry (which has been happening for a number of years) but also now academic studies (investigator lead trials) will be subject to GCP adherence and audit. For academia and private research, the imposition of such strict regulations could signal the end of private research. Indeed action groups are already mobilised and websites are demonstrating reasons and reluctance for the same level of legislation for industry and pure research.

Naturally, this must be measured against ensuring patient safety and the aim of the Directive as a whole is to ensure a standard of patient protection is available uniformly across Europe through legislative and guidance documentation and inspection.

ETHICS COMMITTEES

Ethics committees will now receive more ADR data to comprehend

There are also responsibilities placed upon the ethics members regarding safety. Two important changes have occurred.

The first is more practical than intellectual. The Directive has now stated that all ethics committees should receive all suspected unexpected fatal/life-threatening and serious ADRs within seven and 15 days respectively. This means effectively the ethics committee will receive the reports at the same time as the agencies; follow-up reports likewise. The rationale for this has not been explained. The provision of a timeline for companies to get reports to the committees within these timeframes becomes something of a logistics exercise as well as potentially an auditable item. How would a company know if it got the report to the ethics committee within the specified timelines? Certainly, it is possible to send all reports recorded delivery, but this is a very costly exercise in order to verify receipt on time.

A realisation that this approach could result in a large amount of paper finding its way to the committees resulted in revision of final draft guidance documentation such that it was proposed that 'possibly' ethics committees could receive only those reports originating in to their own country and a quarterly line-listing of all other SUSARs that occurred outside their own country, thereby reducing the amount of paper landing on their desks while at the same time providing full safety information on what is happening with the IMP elsewhere via a line-listing. This still places a logistical headache back to the sponsor on how they would devise such a report for the various ethics committees throughout Europe and a scheduling exercise on producing quarterly reports. Also, the use of the term 'possibly' means that this is not mandatory for various countries and so opens up the prospect that countries will adopt different strategies.

Ethics committees are also to review the benefit/risk of the IMP on an ongoing basis. As stated earlier, the methodology for signal analysis and risk does not just relate to adverse events already assessed as related to therapy but also interrogation of the safety database for other events that may (because of

increased product knowledge) now be regarded as related. Also, the identification of such signals and the risk thereof is a very complex process requiring a safety review extending to preclinical findings as well as a total overview of the safety data and performing complex algorithms looking at exposure and subpopulations. The expectation that ethics committees can review this from line-listings is probably unrealistic. This does not preclude ethics committees from raising safety questions for the sponsor to answer, but the responsibility to proactively assess safety should be the primary role of the sponsor.

PRODUCT DICTIONARY DATABASE

Another requirement of the EU Directive has also appeared in the final guidance notes and this is the EU-specific requirement to register the IMP on a product database. This requirement has been proposed following a recommendation that was made for the post-marketing arena. Indeed marketing authorisation holders (MAHs) were requested to provide details of all of their products on the product database by September 2002. This requirement has still not been fulfilled by many MAHs, but the request for such information to be registered remains. The product when registered is given a unique number. The concept is that the product dictionary will capture the changes to the product (constituents) throughout its development life cycle. During the development life cycle, the IMP may change its constituents, strength and presentation a number of times before the final formulation is determined. All of these changes must be recorded on the product dictionary database. The product dictionary is, however, an EU requirement only and so will only include products being developed or registered in Europe. Without an international initiative to make this requirement a global one, this will be an additional burden for companies with products in the EU. The requirement also places additional resource in registering the products (investigational or marketed) onto the database and then maintain the database with any product changes.

The EU product dictionary database is intended to store information concerning the clinical trial product

THE FUTURE

Are there any outstanding issues to resolve with the Directive now that national implementation in May 2004 has occurred? There are practical aspects regarding the implementation that still have to be overcome. The SUSAR and EudraCT databases are not yet fully operational. The EudraCT database is capable of generating the important EudraCT number, but other functionality mentioned in the guidance notes is not yet available.

Both databases will require pilot programmes in order to test that the systems are working properly. The SUSAR database (which will be very similar to the Eudravigilance safety database) will also require validation. The Eudravigilance database was due for implementation in January 2003 but is still not fully implemented in Europe the latest date for electronic reporting being obligatory within legislation is November 2005) and various member states are not ready to receive electronic submissions.

Additionally, companies had to undergo a registration process for the pilot programme and undertake a three month transitional period from paper to electronic reporting (dual reporting) until acceptance that the system (and the company) was working satisfactorily. With this knowledge, it is not unreasonable to assume that a similar process will be required for the electronic submission of SUSARs. It is not possible for routine electronic submission of SUSARs yet within Europe.

The acquisition of new member states and the adoption of EU pharmaceutical regulations will also provide challenges in incorporating full EU harmonisation. Indeed, to facilitate the transition, new member states are working with existing member states to introduce the necessary

infrastructure to make joining the EU a smooth process.

Ethics committees also will face challenges in implementing and maintaining approvals with the new timelines as well as their increasing role in the monitoring and deliberations concerning safety and risk/benefit.

Finally, the aim of the EU Clinical Trials Directive was to unify the various processes for conduct of clinical trials in Europe. The lack of uniformity was highlighted in the CIOMS V Working Group and clinical trial conduct is to be a topic of CIOMS VI. The national implementation of the Directive relies on all member states *only* implementing what is in the Directive and not adding on top additional national requirements, otherwise all the Directive will do is set a minimum standard for all member states to achieve and not the consistency that was intended.

Challenges lay ahead, not least the national interpretation and implementation of the EU Directive in the 25 member states

Challenges facing industry will be the revision in current practices to the new required legislation, SOPs and training of clinical, pharmacovigilance, quality assurance, regulatory and medical affairs staff in order that everyone is aware of their new roles in order to fulfil the new requirements.

Academia and private research have more to implement in order to be compliant with the Directive, especially since industry has long been following GCP (GCP current draft of the Directive issued July 2004), good laboratory practice (GLP) and GMP requirements. Indeed, the strength of feeling regarding the inability to implement so quickly the requirements the Directive demands for such research has resulted in action groups forming on the internet to discuss the effect on private research. It is thought that damage will be caused to research in general in the European arena, with dire predictions that private research will look elsewhere (USA) in order to continue, resulting in a brain drain and loss of innovative research.

It is fair to say that there is still much more regarding the EU Clinical Trials Directive to be discussed, and the possibilities of amendments to the Directive after May 2004 cannot be ruled out in order that the Directive can be operationally achieved. Certainly, changes are an inevitability of the Directive implementation, but the lack of the Directive would equally have caused more disruption in a 25 member state union each with a myriad of differing national laws.