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Review

Guidelines from the International Conference on Harmonisation (ICH)☆

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Abstract

This article describes the development of international guidance on registration of technical dossiers supporting applications to market medicinal products. Aspects of guidance of particular relevance to the use of NMR spectroscopy in drug development and control are discussed.

Keywords: International Conference on Harmonisation; NMR spectroscopy; Specifications; Analytical validation; Impurities stability

Contents

The increasing globalisation of the pharmaceutical industry is a well-recognised phenomenon. In parallel to the development of medicinal products for use world-wide, there has been a growing impetus to harmonise the requirements for registering these products with regulatory authorities in different regions. Whilst such harmonisation avoids the duplication of work required for registering new medicinal products and is of importance to the pharmaceutical industry to reduce the cost of research and development, it also meets concerns over unnecessary experimentation and the rising cost of healthcare. Furthermore, it may allow patients faster access to new medicines whilst ensuring that they are safe, efficacious and of suitable quality—the aim of regulatory authorities in protecting public health.

The necessity for international regulatory guidance was recognised in the 1980s, with the successful single market created by the European Community at that time setting an example of what could be achieved. Europe, Japan and the United States had begun bilateral discussions on

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the possibilities of harmonisation but specific plans were not initiated until 1989 at a conference organised by the World Health Organisation (WHO) for Drug Regulatory Authorities. Following an approach to pharmaceutical manufacturers, the concept of an international conference on harmonisation was born and discussed in detail at a meeting between regulatory authorities and research-based industry representatives in 1990. A Steering Committee was established at that time. The International Conference on Harmonisation of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) which finally developed is a tripartite body sponsored by regulators and pharmaceutical industry from the three major pharmaceutical markets: the United States (US), European Union (EU) and Japan. As well as the six representatives from regulatory authorities and industry in these three regions, the ICH Steering Committee includes observers from WHO, Health Canada and the European Free Trade Association (EFTA). The work of the Steering Committee is supported by a Secretariat provided by the International Federation of Pharmaceutical Manufacturers Association (IFPMA).

The first meeting of ICH was held in 1991 and although ICH has become synonymous with the process of harmonisation, conferences have been arranged since then at two or, latterly, 3-year intervals together with regional workshops. The Steering Committee is responsible for identifying and approving topics for which harmonised guidelines are then developed. These guidelines can be obtained from the ICH web-site (www.ich.org) and are grouped under the headings *Efficacy* (clinical testing and safety monitoring), *Safety* (preclinical toxicity), *Quality* (pharmaceutical development and specifications) and *Multidisciplinary* (including regulatory communication).

1. The ICH process

There are five stages in the ICH process for developing a new guideline (denoted a "major topic"), represented in Fig. 1. The process starts with consideration of the new topic and development of a consensus by the relevant Expert Working Group (EWG). The EWG members are nominated from the regulatory and industrial bodies in the three regions. The draft consensus resulting from the EWG is then released by the ICH Steering Committee for wider consultation in the three sponsoring regions. Comments from other geographical areas are received through IFPMA and WHO contacts. The comments received are consolidated and the final guideline is issued for adoption and implementation in the three regions. Thus, in Europe, the guidelines are formally adopted by the Committee for Medicinal Products for Human Use, CHMP (previously Committee for Proprietary Medicinal Products, CPMP).

Revisions to existing guidelines are dealt with as a "minor" initiative by an abbreviated maintenance process. Proposals are made by maintenance contacts in the six contributing parties and are either accepted immediately or proceed through a Step 2 consultation process.

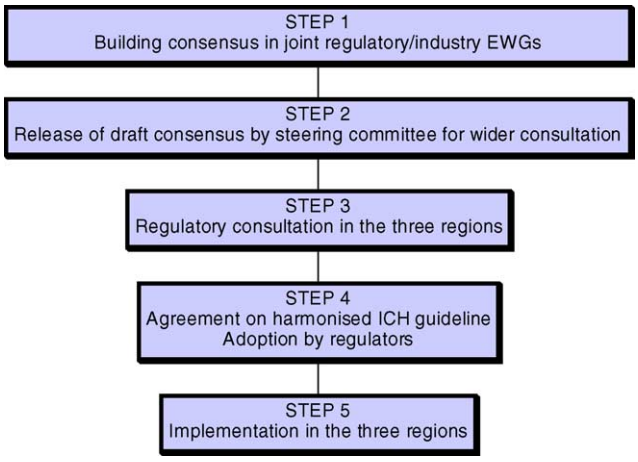

Fig. 1. ICH process for developing harmonised guidelines.

Initially ICH concentrated on producing guidelines on various specific technical aspects of drug registration, in particular relating to quality, pre-clinical safety and efficacy. However, its interests have since widened and it has now produced guidance on a Common Technical Document (CTD) which is being used for registration in the three participating regions.

2. The Common Technical Document

ICH Topic M4 has been the ICH's most ambitious undertaking, aiming as it has to provide the basis for a single set of registration documents to support an application for marketing authorisation in any of the three ICH regions. It is closely linked to Topic M2 on electronic submission of documents which has set out standards to allow data interchange between industry and regulatory agencies. There are differences in regulatory practice in the three regions; in particular in the way authorities interact with the drug development process, which provided considerable hurdles to be overcome by the harmonisation process. The final CTD was completed in November 2000 with a date for regulatory implementation of July 2003. The use of the CTD structure for registration dossiers has been highly recommended in the US since July 2003 but is mandatory in the EU and Japan for new drug applications. Topic M2 was originally approved at Step 4 in October 2003 but has been updated subsequently following on-going support work.

The CTD provides detailed instructions for the format of a registration dossier to accompany an application for a marketing authorisation and the nature of the contents. However, the actual contents may vary in order to satisfy regional requirements. The EWG for the Common Technical Document was extended to include the observers to ICH and representatives of the generics industry and manufacturers of products for self-medication so that as wide a consensus as possible could

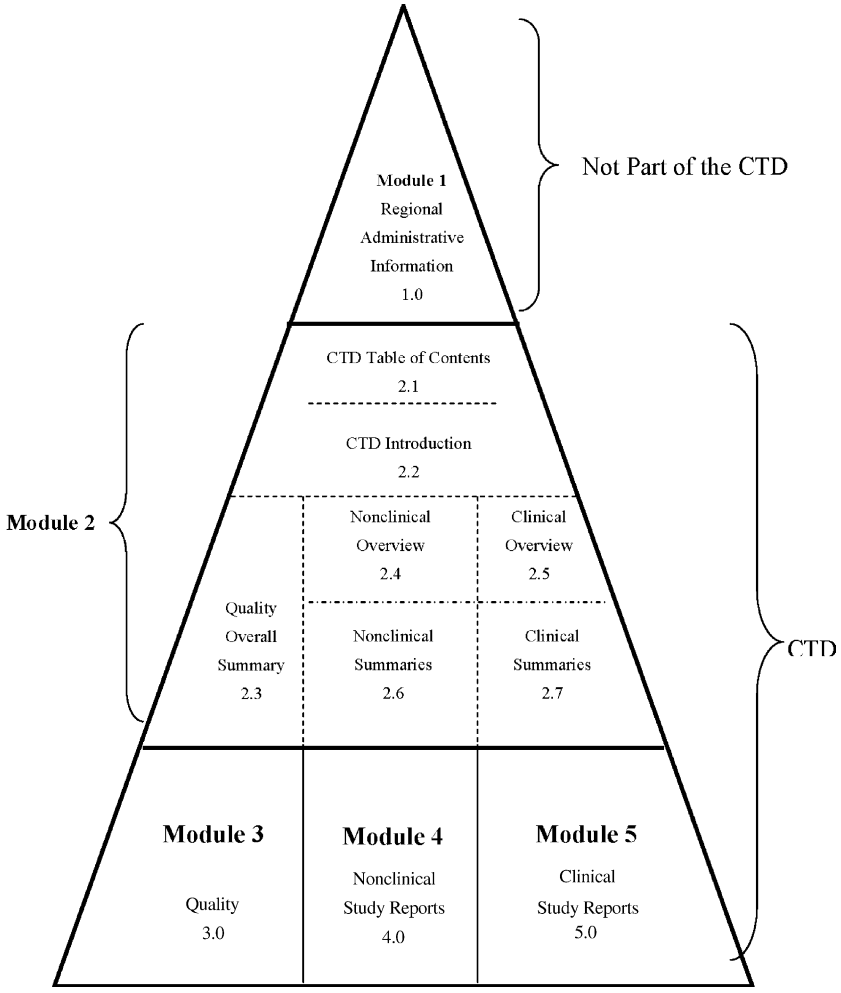

Fig. 2. Diagrammatic representation of the organisation of the CTD.

be achieved. The CTD has a modular structure depicted in Fig. 2 with associated tables of contents (TOC) which also give cross-references to appropriate harmonised guidelines. Whilst these guidelines are intended to be applied to new drug registrations, the principles can be applied to existing drugs for the purposes of maintaining and updating regulatory dossiers. Technical guidelines are generally recommendations and not legally binding. However, any deviations from guidelines should be carefully explained and justified to the regulatory authorities by applicants.

Module 3 contains all the information relating to the quality of the product and analytical techniques associated with monitoring the quality. Thus, quantitative NMR techniques used in product development or its quality control will generally be described here. The contents of Module 3 and relevant ICH guidelines are listed in Table 1.

3. Quality guidelines

There are eight quality topics under the auspices of ICH, including one in the planning stages (Table 2), each with one or more associated guidelines. Some of these are described in more detail below where they are of relevance to the use of quantitative NMR in the drug registration process. The technical guidelines discussed relate to specifications and tests (Q6), impurities (Q3), validation of analytical methods (Q2) and stability (Q1). ICH work on pharmacopoeial harmonisation will also be mentioned.

4. Specifications and tests

Specifications, comprising sets of test procedures and acceptance criteria, are the fundamental basis for the control of the quality of either a drug substance or a medicinal product both at release and during its shelf life. ICH Topic Q6A *Specifications: Test Procedures and Acceptance Criteria for new drug substances and new drug products: Chemical Substances* reached Step 4 in October 1999 and was approved by the CPMP in November 1999 (CPMP/ICH/367/96) with a date of May 2000 (Step 5) for coming into operation in the EU. It was published in the US Federal Register by the Food and Drug Administration (FDA) in December 2000

Table 1
Contents of Module 3 of the ICH CTD

CTD section number	CTD section heading	Relevant reference ICH guidelines (chemical substances)
3.1	Table of contents of Module 3	
3.2	Body of data	
3.2.S	Drug substance (name, manufacturer)	
3.2.S.1	General information	Q6A
3.2.S.2	Manufacture	Q3A, Q6A and Q6B
3.2.S.3	Characterisation	Q3A, Q3C and Q6A
3.2.S.4	Control of drug substance	Q2A, Q2B, Q3A, Q3C and Q6A
3.2.S.5	Reference standards or materials	Q6A
3.2.S.6	Container closure system	
3.2.S.7	Stability	Q1A, Q1B, Q2A and Q2B
3.2.P	Drug product (name, dosage form)	
3.2.P.1	Description and composition of the drug product	Q6A
3.2.P.2	Pharmaceutical development	Q6A, Q8 (planned)
3.2.P.3	Manufacture	Q2A, Q2B, Q6A
3.2.P.4	Control of excipients	Q2A, Q2B, Q3C and Q6A
3.2.P.5	Control of drug product	Q2A, Q2B, Q3B, Q3C and Q6A
3.2.P.7	Container closure system	
3.2.P.8	Stability	Q1A, Q1B, Q2A, Q3B and Q6A
3.2.A	Appendices	
3.2.A.1	Facilities and equipment	
3.2.A.2	Adventitious agents safety evaluation	
3.2.A.3	Excipients	
3.2.R	Regional information	
3.3	Literature references	

Table 2
ICH quality topics

Q1A–F	Stability
Q2A–B	Analytical validation
Q3A–C	Impurities
Q4A–B	Pharmacopoeias
Q5A–F	Biotechnological products
Q6A–B	Specifications
Q7A	Good manufacturing practice
Q8 (planned)	Pharmaceutical development

and adopted by the Ministry of Health, Labor and Welfare (MHLW) in Japan in May 2001. It provides guidance on the selection of test procedures and the setting and justification of acceptance criteria for new drug substances of synthetic chemical origin that have not been previously registered in the EU, Japan or US, and likewise for corresponding drug products. Detailed recommendations are made regarding the specifications for active ingredients and different types of dosage forms. ICH Topic Q6B deals with products of biotechnology which are not considered further here.

Table 3
Summary of tests required in specifications

Drug substances	Drug products
Universal tests	
Description	
Identification	
Assay	
Impurities	
Specific tests	
Physicochemical properties	As listed for
Particle size	Solid oral dosage forms
Polymorphic forms	Oral liquids
Tests for chirality	Parenteral products
Water content	
Inorganic impurities	
Microbial limits	

The considerable guidance, which already existed in the three participating regions, was taken into account during the development of the Q6A guideline. Guidance on specifications is divided into universal tests and criteria which are considered generally applicable to all new substances/products and specific tests and criteria which may need to be addressed on a case-by-case basis when they have an impact on the quality for batch control (Table 3). Tests are expected to follow the ICH guidelines on analytical validation and impurities are the subject of separate guidance—these are discussed below.

NMR has been used as an identity test in drug substance specifications with ^{1}H, ^{13}C or multinuclear spectroscopy being applied as appropriate. Identification of the drug substance is included in the universal category and such a test must be able discriminate between compounds of closely related structure which are likely to be present. Although there are sensitivity issues and instrumentation requires significant investment, there are some circumstances in which the power of NMR spectroscopy for structural discrimination means it is the best choice for an identity test. Solid-state NMR is also a powerful tool in the identification of polymorphic forms which may have a significant impact on the behaviour of the drug substance in the medicinal product.

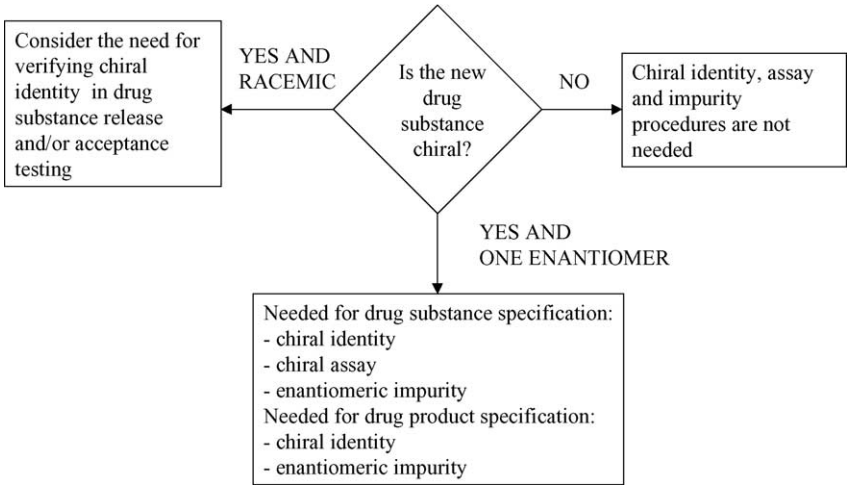

Fig. 3. Establishing specifications for chiral new drug substances and new medicinal products containing chiral drug substances.

5. Chiral drug substances

That chiral substances may need specific identification testing or performance of a chiral assay for successful identification is acknowledged by the guideline. It is worth considering chiral substances in more detail as NMR has been such a successful tool for characterising these compounds. Tests for chiral drug substances are included in the category of specific tests/criteria. A decision tree (Fig. 3) summarises when and if chiral identity tests, impurity tests and assays may be needed in drug substance and finished product specifications. For a drug substance, an identity test should be capable of distinguishing between the enantiomers and the racemate for a drug substance developed as a single enantiomer. A chiral assay or enantiomeric impurity procedure may serve to provide a chiral identity test. When the active ingredient is a racemate, a stereospecific test is appropriate where there is a significant possibility that substitution of an enantiomer for a racemate may occur or when preferential crystallisation may lead to unintentional production of a non-racemic mixture. Such a test is generally not needed in the finished product specification if there is insignificant racemisation during manufacture of the dosage form or on storage and a test is included in the drug substance specification. If the opposite enantiomer is formed on storage then a chiral assay or enantiomeric impurity testing will serve to identify the substance as well.

With respect to impurities, it is acknowledged that, where the substance is predominantly one enantiomer, the opposite isomer is excluded from the thresholds given in the ICH guideline on impurities (see below) because of practical difficulties in quantification at the recommended levels. Otherwise, it is expected that the principles of that guidance apply. The guideline allows that appropriate testing of a starting material or intermediate, with suitable justification from studies conducted during development, could give assurance of control. This approach may necessary, for example, when there are multiple chiral centres present in the drug molecule. Control of the other enantiomer in the finished product is needed unless racemisation during manufacture of the dosage form or on storage is insignificant. The procedure used may be the same as the assay or it may be separate.

Determination of the drug substance is expected to be enantioselective and this may be achieved by including a chiral assay in the specification or an achiral assay together with appropriate methods of controlling the enantiomeric impurity. For a drug product where racemisation does not occur during manufacture or storage, an achiral assay may suffice. If racemisation does happen, then a chiral assay should be used or an achiral method combined with a validated procedure to control the presence of the other enantiomer.

6. Control of impurities

Two ICH guidelines on impurities are discussed here: Topics Q3A makes recommendations on *Impurities in new drug substances* and Topic Q3B on *Impurities in new medicinal products*. In Europe, the guidelines were approved, respectively, as CPMP/ICH/142/95 and its Annex CPMP/ICH/282/95 in May 1995. Revisions to these the drug substance guideline was made in February 2002 and mainly affected the expression of threshold levels and harmonisation with Q3B. The revised text was adopted in the EU in March 2003 (CPMP/ICH/2737/99), in Japan in December 2002 and in the US in February 2003. Revisions to Q3B were made in February 2003, being adopted in the EU, Japan and the US in March, June and November of that year, respectively.

There are two aspects of control of impurities: firstly, their chemical classification and identification and secondly, assessment of their safety at the level imposed by the drug substance specification. The latter is the process of

Table 4
Control of impurities: thresholds for degradation products in new drug substances (a) and products (b)

Maximum daily dose of the drug substance (g/day)	Reporting threshold (%)	Identification threshold	Qualification threshold
(a) ICH Q3A			
≥2	0.05	0.10% or 1.0 mg per day intake (whichever is lower)	0.15% or 1.0 mg per day intake (whichever is lower)
>2	0.03	0.05%	0.05%

Type of threshold	Maximum daily dose	Threshold
(b) ICH Q3B		
Reporting	≤1 g	0.1%
	>1 g	0.05%
Identification	<1 mg	1.0% or 5 μg TDI, whichever is lower
	1–10 mg	0.5% or 20 μg TDI, whichever is lower
	>10 mg–2 g	0.2% or 2 mg TDI, whichever is lower
	>2 g	0.10%
Qualification	<10 mg	1.0% or 50 μg TDI, whichever is lower
	10–100 mg	0.5% or 200 μg TDI, whichever is lower
	>100 mg–2 g	0.2% or 3 mg TDI, whichever is lower
	>2 g	0.10%

qualification which is discussed further below. As noted above, enantiomeric impurities are excluded from the impurities guideline, but the principles expressed are expected to apply.

Impurities may be organic, inorganic, such as catalysts, or residual solvents. These last are dealt with by a separate ICH guideline (Topic Q3C). Any differences between the impurity profile of the drug substance intended for marketing and that used in development should be discussed. Organic impurities may consist of starting materials, by-products, intermediates, degradation products or other substances used in the synthetic process. NMR is the most likely to be used in the structural characterisation of substances related to the drug substance whether arising from the synthetic process or from degradation. The guideline lays down a series of thresholds (Table 4) which are dependent on the daily dose of the drug. Substances which are present above the "reporting threshold" must be recorded but they do not have to be characterised unless they are present in amounts greater than the "identification threshold". Justification must be provided if impurities remain unidentified and they should still be controlled in the specification as a "known" impurity.

Qualification is the process by which the biological safety of an individual impurity, or an impurity profile, is established at a particular level. Organic impurities present above the "qualification threshold" must undergo this process or efforts be made to reduce the amount appearing in the drug substance. The guideline contains a decision tree to assist in judging the need to identify and qualify impurities. If the drug substance containing the impurity at a particular level has been subjected to adequate safety and/or clinical studies, then that level is considered to be qualified. Lower or higher qualification thresholds may be appropriate for certain classes of drugs, for example, particularly toxic impurities may need lower thresholds. Impurities which are also metabolites need no further qualification as their effects would have been taken into account along with administration of the drug substance itself. Similar qualification of enantiomeric impurities by their presence in batches of drug substance used in safety and/or clinical studies would be expected, although the actual thresholds stated in the guideline would not necessarily apply.

Table 5
Categories of organic impurities to be listed in specifications

Drug substance specification	Drug product specification
Each specified identified impurity	Each specified identified degradation product
Each specified unidentified impurity	Each specified unidentified degradation product
Any unspecified impurity with an acceptance criterion of not more than the identification threshold	Any unspecified degradation product with an acceptance criterion of not more than the identification threshold
Total impurities	Total degradation products

The guideline on impurities in new drug products (ICH Topic Q3B) parallels the drug substance text but the designated thresholds concern only degradation products. The thresholds should be applied to the product at the end of its shelf-life, as that is when the greatest level of degradation is expected to have occurred.

Together with batch analysis data, the identification and qualification studies should be used to justify the limits for impurities in the categories given in Table 5 as appropriate. The limits of detection and quantitation used in the methods to analyse the impurity content of the batches of drug substance used in pre-clinical and clinical studies and in the final specifications must be taken into account when setting impurity limits. It is not usually necessary to include impurities associated with the synthesis of the active ingredient in the finished product specification as they should already be controlled in the drug substance.

7. Analytical validation

There are two ICH guidelines on analytical validation. The first provides a glossary of terms and the second addresses methodology. The first guideline, ICH Topic Q2A *Validation of analytical procedures: Definitions and terminology*, reached Step 4 in October 1994. It sought only to present a collection of terms and definitions and not to provide direction on how to accomplish validation. The guideline was

Table 6
Characteristics of analytical procedures requiring validation (indicated by a tick (√))

	Identity	Control of impurities		Assay
		Quantification	Limit test	
Accuracy and precision		√		√
Specificity	√	√	√	√
Limit of detection		√	√	
Limit of quantitation		√		
Linearity and range		√		√

intended to bridge the differences which could exist between the various compendia and regulators in the three regions of the ICH. In the EU, the guideline was approved by the CPMP in November 1994 (CPMP/III/5626/93) and came into operation in June 1995. The FDA incorporated the ICH definitions of analytical terms into its guidance on validation of chromatographic methods in November 1994 and published the guideline in March 1995. In Japan, the guideline was adopted by the MHLW in July 1995.

The guideline states that the objective of validation is to demonstrate that an analytical method is fit for its purpose and summarises the characteristics required of tests for identification, control of impurities and assay procedures (Table 6). Requirements for other analytical procedures may be added in due course.

Assays may be applied to the active moiety in the drug substance or drug product or to other selected components of the product. They are used for content/potency determinations and for measurement of dissolution. Precision includes repeatability (intra-assay precision) and intermediate precision (within laboratory) except the latter is not required where reproducibility (inter-laboratory) has been performed. If there is lack of specificity in one analytical procedure, compensation by other supporting methods is allowed. The characteristics listed in the table are considered typical but allowance is made for dealing with exceptions on a case-by-case basis. Robustness is not listed but should be considered at an appropriate stage in development. Revalidation of analytical procedures is required following changes in the synthesis of a drug substance, composition of the finished product or in the analytical procedure.

The second guideline, ICH Topic Q2B, *Validation of analytical procedures: Methodology*, reached Step 4 in November 1996, was approved by the CPMP in Europe in December 1996 (CPMP/ICH/281/95) and came into operation in June 1997. It was published in the US in May 1997 and adopted by the MHLW in October of the same year. It is complementary to the first guideline and provides some guidance and recommendations on acceptable methods for validating the characteristics of analytical procedure. An indication of the data which should be provided in an application for a marketing authorisation is given. It discusses the following characteristics separately: specificity; linearity; range; accuracy; precision; detection limit; quantitation limit; robustness and system suitability testing.

Identity tests need to be specific to ensure lack of interference from related substances or other impurities. This is less of a problem when NMR techniques are used due to their ability to distinguish between even closely related structures. Indeed, the specificity of NMR has been used to advantage in validating other analytical methods, for example, in ensuring peak purity in chromatography. Hyphenated techniques such as HPLC-NMR are useful in this regard. NMR has traditionally suffered from lack of sensitivity and therefore, its use in quantitative analytical methods has been limited. However, modern developments mean that it is becoming a viable option in particular cases either for assay or control of impurities, in which case the method should be validated according to the principles described above. The value of NMR for related substances determinations

Table 7
ICH stability testing guidelines

Topic	Title	Date of Step 4 adoption	Date of Step 5 regional approval
Q1A	Stability testing of new drug substances and products	October 1993	Revision 2
		Revision 1 November 2000	EU: March 2003
		Revision 2 February 2003	Japan: June 2003
			US: November 2003
Q1B	Photostability testing of new drug substances and products	November 1996	EU: December 1996
			Japan: May 97
			US: May 1997
Q1C	Stability testing of new dosage forms (Annex to Q1A)	November 1996	EU: December 1996
			Japan: May 97
			US: May 1997
Q1D	Bracketing and matrixing designs in stability testing of new drug substances and products	February 2002	EU: February 2002
			Japan: July 2002
			US: January 2003
Q1E	Evaluation for stability	February 2003	EU: March 2003
			Japan: June 2003
			US: June 2004
Q1F	Stability data package for registration applications in climatic zones III and IV	February 2003	EU: March 2003
			Japan: June 2003
			US: November 2003

is its ability to both identify and quantify compounds simultaneously.

8. Stability

Stability studies are used to establish the re-test period for the active ingredient – that is the length of time it can be stored and used without analysing immediately before use – and the shelf life of the finished product. The release and shelf life specifications for the product may differ to accommodate degradation of the active ingredient or other acceptable changes which may occur on storage. ICH has published a set of guidelines relating to the stability studies expected for new drug substances and products (Table 7).

NMR plays a part in stability studies if used in either the drug substance or finished product specifications or as an additional stability-indicating method used in the protocol. An example of the latter is the use of solid-state NMR methods to monitor the polymorphic form of the drug substance on storage. If stability in this regard is demonstrated, then the test does not need to appear in the final registered specification. The main guideline, ICH Topic Q1A, *Stability testing of new drug substances and products* was initially adopted in 1993 but has since been updated to accommodate the additional climatic zones which are the subject of Topic Q1F. The stability of the drug substance or product under standard long-term and accelerated storage conditions dictates the re-test period or shelf life, respectively, that can be claimed for each. Recommendations are made on the number of batches, testing frequency and evaluation of results (further detailed guidance on this subject being given in Topic Q1F).

9. Pharmacopoeial harmonisation

Pharmacopoeial harmonisation under the auspices of the Pharmacopoeial Discussion Group (PDG) started before ICH and the two bodies have maintained close links. Stimulated by the publication of Topic Q6 on specifications and tests, ICH Topic Q4B, *Regulatory acceptance of pharmacopoeial interchangeability* was established in November 2003 with the aim of facilitating regulatory implementation of harmonised pharmacopoeial monographs. The work of the Topic Q4B EWG centres on providing clear information of the status of harmonised texts in the different regions by working with the PDG.

10. Concluding remarks

The success of ICH has been based on the achievement of scientific consensus and the commitment of the three participating regulatory authorities to implement harmonised guidelines. Having succeeded in harmonising the format of the registration dossier and its electronic counterpart, ICH has declared a focussed programme of implementation and maintenance to ensure that the process keeps pace with the changing international environment. Risk management in the post-marketing arena has been identified as a topic for particular attention which would benefit public health on an international basis.

The work of ICH on efficacy has probably had the most significant impact on industry, if it is considered that clinical trials are the most expensive and complex part of drug development. However, ICH quality guidelines have had their own role to play in reducing the amount of duplicate testing in pharmaceutical development, in particular, in the areas of setting impurity limits and stability testing. The latter will also have an impact on post-authorisation changes relating to manufacturing and packaging which need to be supported by on-going stability studies [1].

ICH is also aware of the need to disseminate information beyond the three participating regions and the role of the WHO as an observer is important in this regard. ICH has also set up a Global Cooperation Group whose purpose is to make available information on ICH, its activities and guidelines to any country or company on request. The six ICH Steering Group parties and observers contribute to the GCP and organisations representing other regional harmonisation initiatives have also been invited to participate. Thus, ICH in the future is likely to have a much wider impact world-wide than just the three original sponsor regions.

Reference

[1] C. Nutley, The Value and Benefits of ICH to Industry, IFPMA, 2000, http://www.ich.org.