Medical writing for generics throughout the life cycle

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Abstract
Medical writing plays an integral part in the pharmaceutical industry, be it for originator or generic drug companies. Most writers are working for medium to large research-based companies. However, even for generic drug firms many documents need to be composed, preferably by or with the help of a medical writer. This article aims to familiarise the reader with the usual terminology and relevant guidelines. Key documents throughout the entire life cycle of generic medicinal products are described, starting with the clinical documents during the development process, continuing with required support for the authorisation process, and concluding with post-marketing material.

In the pharmaceutical environment there are two types of companies: originator and generic companies. To put it in a nutshell: the former typically heavily invest in research and development to produce new drug products while the latter reproduce the originator companies' ideas. Generic medicines may only be marketed after the original patent has expired. This is usually 10 years from the date of first authorisation.

Because the manufacturers of generic drugs have not had the expenses of developing a new drug, their products are cheaper. Unlike their larger originator counterparts, generic companies are typically smaller and usually don't have their own clinical and in-house writing capabilities. Therefore, they often need to outsource these activities.

It's probably fair to say that most medical writing is done for originator medicinal products. If you have only been involved with new chemical entities, you may ask yourself what medical writing for generics has in store. The legal basis of marketing authorisation applications is associated with specific data requirements and will heavily influence the types of documents written, as well as the content of the submission dossier. In this introduction section I will give you a very short guide to "all you need to know about generic medicinal products" before we dive headfirst into the practical part of medical writing for generics.

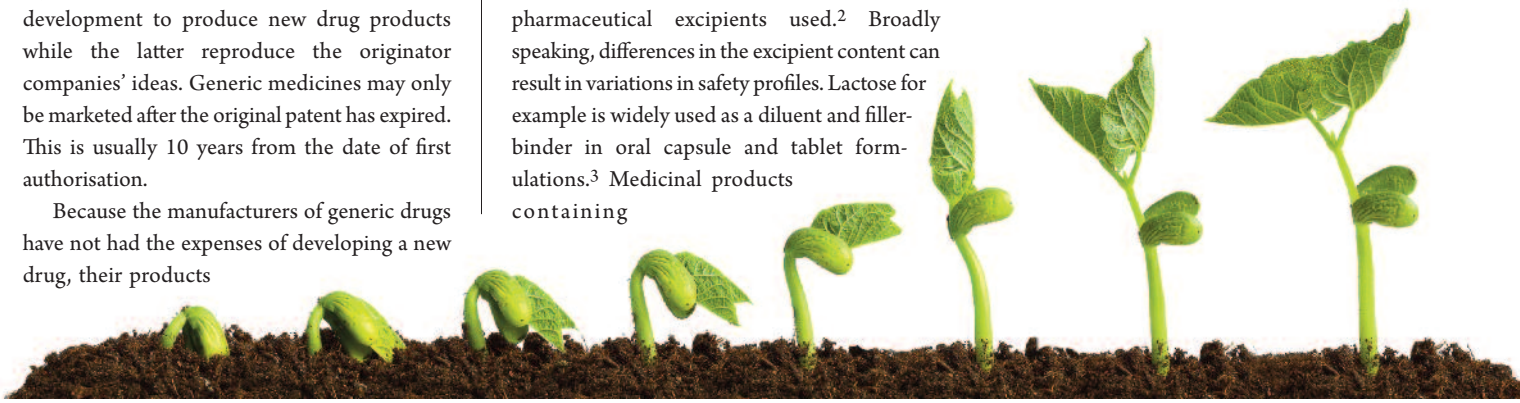
A generic medicine is developed to be the same as the reference medicine, which has already been authorised on the basis of a complete dossier. If the marketing authorisation application for a generic medicinal product can demonstrate bioequivalence, no additional preclinical tests or clinical trials are needed. Instead, the application refers to the preclinical and clinical data for the reference product.

According to the definition given by the EMA, "a generic medicine contains the same active substance(s) as the reference medicine, and it is used at the same dose(s) to treat the same disease(s). However, a generic medicine's inactive ingredients, name, appearance and packaging can be different."[1] As the inactive ingredients do not have to be identical, the generic medicinal product may have different side effects or contraindications based on the pharmaceutical excipients used.[2] Broadly speaking, differences in the excipient content can result in variations in safety profiles. Lactose for example is widely used as a diluent and filler-binder in oral capsule and tablet formulations.[3] Medicinal products containing lactose must carry a labelling warning according to the European Commission guideline on "Excipients in the labelling and package leaflet of medicinal products for human use".[4] Therefore, any medical writer preparing the submission documentation for a generic medicinal product should be aware of differences in composition in relation to the originator product. Any differences regarding the excipients, including possible safety-related issues, should be discussed in the dossier.

According to Article 10(1) of Directive 2001/83/EC,[5] bioequivalence to the reference medicine must be demonstrated. In some cases, bioequivalence studies are not mandatory, e.g., for simple oral solutions or aqueous solutions for intravenous or intramuscular injection, provided they contain the same active substance in the same concentration as the currently authorised product.[6]

The following sections aim to guide you through the whole life cycle of a generic medicinal product, starting with the clinical documents during the development process, continuing with the preparation of the submission dossier, and concluding with post-marketing material (see Table 1 for an overview).

Medical writing during the drug development process
Generating bioavailability (rate and extent of absorption) and bioequivalence study data is a critical step in the development process for a generic drug. Since the EMA (and the FDA for that matter) do no ask for clinical outcome data for the registration of generics, the demonstration of bioequivalence based on pharmacokinetic (PK) criteria is the key component of



therapeutic equivalence. The most important reference source in the EU for the investigation of bioequivalence is EMA guideline CPMP/EWP/QWP/1401/98 Rev. 1.[6] It is, however, always worth checking which guideline(s) apply to the particular characteristics of the medicinal product (e.g., dosage form). Specific recommendations for modified release products, transdermal products, and orally inhaled products are given in various guidelines. Making use of regulatory or scientific advice prior to submission may save the generic company a lot of money and prevent the wrong studies being performed or rejected later during the authorisation process.

Medical writers who already work in the area of clinical trials will be familiar with the documents that are typically needed for bioequivalence studies, such as protocols, informed consent forms, study reports, and manuscripts. Publishing the outcomes of bioequivalence studies is not common practice, although increased transparency is highly desirable considering the number of people treated with generic drugs.[7] Another typical document in clinical research, the Development Safety Update Report, is not required for bioequivalence studies.

Bioequivalence studies are usually randomised, two-period, two-sequence, single-dose crossover trials including a small sample of healthy volunteers. Their aim is to demonstrate that two molecules are chemically bioequivalent based on the following PK criteria: rate of absorption, as determined by the peak plasma concentration (C_{max}), and area under the plasma concentration–time curve from time 0 to end of study (AUC_{0-t}) and to infinity ($AUC_{0-\infty}$). Limits used to conclude bioequivalence are fixed by regulatory agencies (see below).[7]

The report of the bioequivalence study should be written according to ICH E3. It should include evidence that the choice of reference medicinal product is in accordance with Article 10(1) and Article 10(2) of Directive 2001/83/EC.[5,6]

In the bioequivalence assessment of two brands, the 90% confidence interval for the geometric mean ratios of AUC and C_{max} should be contained within the acceptance interval of 80.00-125.00%. For drugs with a narrow therapeutic index (a small window between their effective dose and the dose which has a toxic effect), a tightened acceptance interval of 90.00-111.11% applies. There are further different assessment requirements for highly variable drug

Table 1. Overview of typical documents written for generic medicinal products

Lifecycle stage	Type of document	Type of medical writing required	Nature & content	Applicable guideline
Development	Protocol	Regulatory	Same as for any CT	ICH E6
	Informed consent form	Regulatory	Same as for any CT	ICH E6
	IMPD	Regulatory	Special requirements	EMA/CHMP/QWP/54552 5/2017
	IB	Regulatory	The approved SmPC may be used	ICH E6
	Study report	Regulatory	Full	ICH E3 CPMP/EWP/QWP/1401/98 Rev. 1/ Corr
	Manuscript	MedComms	Same as for any publication	Journal's author guidelines, CONSORT Statement, etc.
Authorisation	Module 1.5.2 Information for Generic, "Hybrid" or Bio-similar Applications	Regulatory	Concise summary document	NTA
	Module 2.4 Non-clinical overview	Regulatory	Bibliographic / Refer to data for reference product	NTA ICH M4
	Module 2.5 Clinical overview	Regulatory	Bibliographic / Refer to data for reference product + information on BE study	NTA ICH M4
	Module 2.7.1	Regulatory	Key document to present BA and BE data	NTA ICH M4
	RMP	PV	Abbreviated	GVP Module V
Post-marketing	ACO	PV	Full, if required (check national requirements)	CMDh Best Practice Guide on the processing of renewals in the MRP / DCP
	PSUR	PV	Full, if required	GVP Module VII ICH E2C(R2)

Abbreviations: ACO, Addendum to the Clinical Overview; BA, bioavailability; BE, bioequivalence; CMDh, Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human; CONSORT, Consolidated Standards of Reporting Trials; CT, clinical trial; DCP, decentralised procedure; GVP, good pharmacovigilance practices; IB, Investigator's brochure; ICH, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; IMPD, Investigational Medicinal Product Dossier; MedComms, medical communications; MRP, mutual recognition procedure; NTA, Notice to Applicants; PSUR, Periodic Safety Update Report; PV, pharmacovigilance; RMP, Risk Management Plan; SmPC, Summary of Product Characteristics

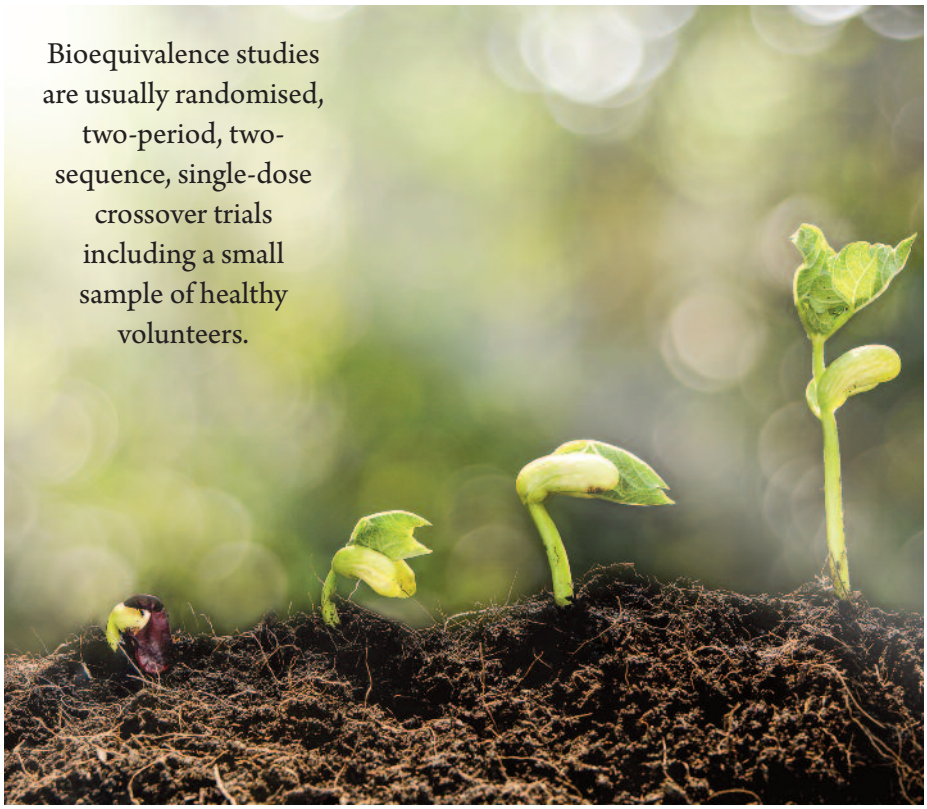
products.[6] The assessors will *always* check whether AUC and C_{max} are within the 90% confidence interval, unless the acceptance intervals have been defined otherwise and justified before the conduct of the study. The regulatory authorities adhere very strictly to the bioequivalence guideline on this point and will generally leave no room for discussion.

One other thing of high importance is the in vitro dissolution of the biobatches. Dissolution testing measures the amount of a given substance that goes into solution per unit time under standardised conditions. It is one of the most important tools to predict the in vivo bioavailability of oral solid dosage forms.[8] Dissolution studies have to be performed using three different buffers (normally pH 1.2, 4.5, and 6.8). However, if the in vitro dissolution studies fail but bioequivalence was demonstrated in vivo, the latter prevails.[6]

As a surrogate for in vivo bioequivalence, the Biopharmaceutics Classification System (BCS)-based biowaiver approach may be used under certain circumstances.[6] According to the BCS, drugs are usually divided into four classes depending on their solubility and their permeation capacity. BCS-based biowaivers can only be applied for highly soluble drug substances with known human absorption and considered not to have a narrow therapeutic index. The EMA accepts BCS-based biowaivers for both BCS class 1 and class 3 immediate-release drug products, which have high solubility and either complete (class 1) or limited (class 3) absorption.[9] The ICH M9 draft guideline on BCS-based biowaivers describes the recommended format and content of documentation to support waivers for bioequivalence studies.[10]

Preparation of the submission dossier

The EU legislation allows for abbreviated applications for generic medicines. The dossier nevertheless needs to follow the requirements set out in the Notice to Applicants (NTA), regulatory guidelines, and the Common Technical Document (CTD) format.[11] Submissions should contain the complete administrative and quality data (Modules 1 and 3) and relevant preclinical and clinical data (Modules 2, 4, and 5). Reference is made to data in the originator product's authorisation application that demonstrate the safety and efficacy of the active molecule. Applicants have to show that the medicinal



product is a generic version of the reference product by summarising the relevant bioavailability and bioequivalence data, as well as by providing information on the qualitative and quantitative composition, the pharmaceutical form, and the safety/efficacy profile.[12] The non-clinical and clinical overviews should focus on particular issues concerning the basis for the application (see below for further information).[13]

Module 1

- Module 1.3.1 (Product information): the EMA has published Quality Review of Documents (QRD) general principles regarding the Summary of Product Characteristics (SmPC) for a generic. The content of the generic's SmPC should be consistent with that of the reference medicinal product *except* for indications or dosage forms still covered by patent law. Any differences in the proposed SmPC or claims not inferred from the composition or other properties of the generic need to be discussed and justified.[14] This should be done in the non-clinical and/or clinical overviews and be substantiated by published literature and/or additional studies.[13]
- Module 1.5.2 (Information for Generic, "Hybrid" or Bio-similar Applications): In a concise document, the grounds and evidence used for demonstrating that the medicinal product is a generic version of the reference medicinal product need to be summarised. The summary should include details on the generic medicinal product, notably its composition and pharmaceutical form and the safety/efficacy profile of the active substance(s) in comparison to the reference medicinal product. Where necessary, details related to bioavailability and bioequivalence of the generic medicinal product should also be included.[13]
- Module 1.8.2 (Risk Management Plan [RMP]): It is expected that the safety specification is the same as that of the reference product. Any deviations need to be properly justified, since regulatory agencies are generally very reluctant to allow discrepancies with approved RMPs. According to the Guideline on good pharmacovigilance practices (GVP) Module V, new marketing authorisation applications for generic medicinal products have abbreviated content requirements (see Table 2).[15] Generic RMPs

will not require RMP Modules SI (Epidemiology of the indication(s) and target population(s)), SII (Non-clinical part of the safety specification), SIII (Clinical trial exposure), SIV (Populations not studied in clinical trials), SV (Post-authorisation experience), and SVI (Additional EU requirements for the safety specification). Furthermore, Module SVII (Identified and potential risks) is only relevant if the originator product does not have an RMP and its safety profile is not published on the CMDh (Co-ordination Group for Mutual Recognition and Decentralised Procedures – Human) website. If more than one list of safety concerns published on the CMDh website applies for the same active substance, the applicant needs to justify the choice of proposed safety concerns in Module SVIII. RMP Part IV (Plans for post-authorisation efficacy studies [PAES]) is only relevant when a PAES was imposed for the originator product. In RMP Part V (Risk minimisation measures) a statement of alignment of safety information in the product information is sufficient.[15]

It is important to point out here that with revision 2 of GVP Module V, the definitions of safety concerns have changed. This poses challenges both for the applicant and the regulatory authorities if the originator RMP was compiled according to revision 1. Different EU member states have taken different approaches to dealing with this situation until all originator RMPs have been updated according to the current definitions. This has led to a situation where different generic products have identified safety concerns that deviate from the reference product. The following principles have been proposed by the Austrian competent authority: for active substances for which there is no innovator or the innovator has no RMP, only safety concerns that have 1. ongoing additional pharmacovigilance activities, 2. ongoing additional risk minimisation measures, or 3. essential targeted questionnaires in place should be listed. For active substances for which there is a centrally authorised generic, the safety profiles of RMPs for subsequent generics should be aligned with the RMP for the centrally authorised generic. This applies to all national (including decentralised or mutual recognition procedure) and centralised marketing authorisation applications.

Module 2

Essential documents for Module 2 are the quality overall summary (Module 2.3), non-clinical overview (Module 2.4), clinical overview (Module 2.5), and Module 2.7.1 of the clinical summaries. The non-clinical summaries and the other modules of the clinical summaries (Modules 2.6.1 to 2.6.7 and 2.7.2 to 2.7.6, respectively) are only mandatory if additional studies have been performed.

As the applicant is not required to provide the results of pre-clinical tests and clinical trials, Modules 2.4 and 2.5 are mainly based on published literature. It is common practice to provide a description and justification of the literature search strategy. All documentation, whether favourable or unfavourable, should be included. A statement on GLP/GCP compliance is usually included in the overviews. In addition, a summary of impurities and relevant decomposition products should be provided.[12]

When different salts, esters, ethers, isomers, mixtures of isomers, complexes, or derivatives of the active substance of the reference medicinal product are used, additional information providing proof that the safety and/or efficacy profile is not different from that of the originator should be submitted.[12]

The results of the bioequivalence studies or a justification (biowaiver) for why studies were not performed should be presented in Module 2.5 and 2.7.1. The objective of Module 2.7.1 is to summarise all relevant information about biopharmaceutic studies and associated analytical methods. Appendix IV[16] of the Guideline on the Investigation of Bioequivalence[6] contains a set of template tables to assist applicants in the preparation of Module 2.7.1 and provides guidance regarding data to be presented. If a BCS-based biowaiver is submitted, Module 2.7.1 should contain a summary of the in vitro dissolution data with a justification for not performing a bioequivalence study and a list of relevant references.

Module 3

The CMC part of the dossier is very similar for generic and originator medicinal products, as quality always needs to be demonstrated. Therefore, a complete Module 3 of the CTD needs to be submitted in accordance with the requirements set out in the NTA. For solid dosage form generic medicinal products, comparative dissolution studies will be provided in this part of the dossier.

Modules 4 and 5

Modules 4 and 5 for generic medicinal products mainly contain bibliographic data, as it is not necessary to provide the results of toxicological and pharmacological tests or of clinical trials. Module 5.3.1 (Comparative Bioavailability and Bioequivalence Study Reports) should contain the results of the bioequivalence studies performed or relevant data justifying the BCS-based biowaiver, if applicable.

Table 2. Summary of minimum RMP requirements for generic medicinal products

Part I	Part II								Part III	Part IV	Part V	Part VI
	SI	SII	SIII	SIV	SV	SVI	SVII	SVIII				
✔	N/A	N/A	N/A	N/A	N/A	N/A	‡	✔	✔	*	†	✔

European Medicines Agency and Heads of Medicines Agencies, 2017[15]

✔ Applicable

N/A Not applicable

‡ Relevant only if the originator product does not have an RMP and its safety profile is not published on the CMDh website

* Relevant only when a post-authorisation efficacy study was imposed for the originator product

† Statement of alignment of safety information in the product information is sufficient

Post-marketing medical writing

Periodic Safety Update Report

According to Directive 2010/84/EU,[17] generic medicinal products are usually exempt from Periodic Safety Update Report (PSUR) submission. However, for some products, the submission of PSURs is a condition of marketing authorisation. In addition, competent authorities are empowered to request the submission of a PSUR at any stage. This could be based on safety concerns relating to the emergence of new data or due to the lack of PSURs when the reference medicinal product is no longer marketed. Evaluation of the literature plays an integral part in the preparation of PSURs. Please note that literature should not only be presented in the PSUR; assessors also want to see a comment or conclusion on the risk-benefit balance. Even if no new literature is found for an active substance, the search terms and databases used should be mentioned in the PSUR.

The list of European Union reference dates specifies the substances for which PSURs for generic medicinal products are required. Do not send PSURs which are not required! However, even where PSURs do not need to be submitted routinely, marketing authorisation holders still need to regularly evaluate the safety of their products and report any new safety information that affects the risk-benefit balance or the product information.[18]

Medical writing for generics poses its own challenges and requires some specialist knowledge.

Medical writers may also be asked to write a PSUR for a marketing authorisation for a generic drug outside of the EU, e.g., in Eastern Europe. If a PSUR is required for a generic drug, the requirements as to the content are the same as for the originator medicinal product.

Addendum to the Clinical Overview

An Addendum to the Clinical Overview (ACO) is submitted during a marketing authorisation renewal and basically follows the same format as a PSUR. The aim is to present all relevant safety and efficacy information since the granting of the marketing authorisation or the last renewal, along with a critical discussion of the risk-benefit balance. For renewals of products authorised under Article 10(1), a shortened procedure can be applied, in which case no ACO needs to be submitted.[19] There are, however, exceptions to this rule. In Austria, for example, an ACO always needs to be submitted for national authorisations or, in the case of a decentralised procedure, if Austria is the Reference Member State. This requirement applies irrespective of the recommendations published in the CMDh Best Practice Guide on the processing of renewals in the mutual recognition and decentralised procedures.[20] It is always worth checking the national requirements! In addition, ACOs are also requested by many national authorities outside the EU. The ACO should cover the period from the date of approval to the date of submission of the renewal. Use GVP Module VII[18] on PSURs as guidance for preparation of the ACO and use the structure given in the CMDh Best Practice Guide.[19]

Other post-marketing documents

Other post-marketing medical writing for generics often involves pharmacovigilance activities, such as updates of RMPs or the preparation of educational materials. The frequency of RMP updates should be proportionate to the risks of the product. RMPs are continually updated throughout the product life cycle, as new information becomes available. Companies need to submit an updated RMP at the request of a competent authority or whenever new information may significantly affect the risk-benefit profile or as a result of an important pharmacovigilance or risk-minimisation milestone being reached. When updating an existing RMP prepared according to revision 1 of GVP Module V, it may be necessary to adapt the safety concerns according to the current definitions (see above).

Conclusion

Medical writing for generics poses its own challenges and requires some specialist knowledge. The skills of a professional medical writer might be repeatedly required throughout the life cycle of a generic medicinal product. Getting familiar with the relevant guidelines, including national requirements, is essential to prepare for this task.

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Conflicts of interest

The author declares no conflicts of interest.

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