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DANISH MEDICINES AGENCY

The Danish Medicines Agency's 2009 API project

- focus on monitoring compliance with the rules by manufacturers of active pharmaceutical ingredients

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Contents

1. Summary

In 2009, the Danish Medicines Agency conducted a survey to examine the extent to which manufacturers of medicinal products comply with their obligation to ensure that the active pharmaceutical ingredients used as raw materials in the manufacture of medicinal products and intermediate products are manufactured in accordance with good manufacturing practice for active pharmaceutical ingredients.

As part of the survey, the Agency has carried out inspections at companies in both Denmark and abroad and has also requested that a number of companies submit samples of medicinal products and samples of active pharmaceutical ingredients as well as relevant written documentation for further control.

The survey confirmed the Agency's presumption that Danish manufacturers of medicinal products, by carrying out regular audits of manufacturers of active pharmaceutical ingredients, to a wide extent meet the requirement of ensuring that the active pharmaceutical ingredients in question are manufactured in accordance with good manufacturing practice.

The survey also identified a number of areas in which the Danish Medicines Agency and the industry in future can improve the existing control of manufacturers of active pharmaceutical ingredients.

Based on the survey, the Agency will launch additional initiatives and projects to ensure more targeted guidance and control within the area of active pharmaceutical ingredients.

2. Introduction

In 2009, the Danish Medicines Agency carried out a project focusing on active pharmaceutical ingredients used as raw materials in the manufacture of medicinal products. During the project, compliance of rules in relation to the manufacture, monitoring and control of the quality of active pharmaceutical ingredients (APIs) was spot checked. The background for the project is a cross-organisational risk project from 2008 which identified a number of risks related to the manufacture and distribution of marketed medicinal products.

The following weighty arguments were presented for initiating a project on APIs:

1) The EU rules on APIs used in the manufacture of medicinal products were implemented in Danish law in December 2005 and can thus be said to be relatively new. Through its regular control, the Agency has observed that several companies have had problems interpreting and complying with this new requirement and lack information about the extent to which the new requirement has had the desired effect.

2) As is the case with other industries, parts of the pharmaceutical industry's production are also moved to companies outside of the EU. As most manufacturers of APIs in non-European countries lack experience in the manufacture of APIs according to European standards, it is a major challenge to ensure that APIs manufactured in these countries are of the right quality. Since 2005, European medicines agencies (including the Danish Medicines Agency) have conducted random inspections of selected API manufacturers – often located in India and China. These random inspections have identified several API manufacturers that have not implemented the requirements of the European regulatory authorities. More specifically, the Danish Medicines Agency has, on several occasions, had to withdraw finished medicinal products, as they contained APIs from API manufacturers with an insufficient level of quality assurance.

3) There is a risk that counterfeit APIs, which even in very small quantities may be harmful to consumers, are introduced in the legal API supply chain and are used in the manufacture of approved medicinal products. In 2008, contaminated APIs of the heparin type manufactured by one or more Chinese API manufacturers caused multiple deaths in the USA. The contaminated heparin was never marketed in Denmark. However, this case does serve as a reminder that the manufacture of APIs should be monitored carefully.

The purpose of the project has been to improve the basis for effective control of the manufacturers, repackaging sites, agents, brokers and distributors[1] of APIs used through collaboration with Danish pharmaceutical companies. It has also been the objective that the knowledge and experience gathered should enable the Danish Medicines Agency to evaluate the level of compliance with the rules and to evaluate the effect of the legislation. Finally, it has been an objective that the Agency, based on the project, should be even better equipped to focus its control on relevant risk areas and medicinal product or company types within the manufacture and handling of APIs.

The project has had two parallel tracks. Control has been carried out of:

- APIs and relevant documentation (checked by the Agency's laboratory); and
- the control by finished product manufacturers of APIs and API manufacturers (checked by the Agency's medicines inspectors).

[1] In this report, API agents, brokers and distributors will collectively be referred to as 'traders'.

3. Legislation

3.1. Rules on the manufacture of medicinal products

The manufacturer of medicinal products (the finished product manufacturer)[2] must ensure that medicinal products covered by a marketing authorisation are in accordance with the manufacturing processes on which the marketing authorisation has been granted. The manufacturer must also ensure that all manufacturing processes are carried out in accordance with good manufacturing practice (GMP) for medicinal products. This follows from section 10(1)(i) and (ii) of the Danish executive order on the manufacturing and import of medicinal products and intermediate products (the GMP order)[3]. Detailed guidelines for good manufacturing practice for medicinal products have been provided in the 'Rules Governing Medicinal Products in the European Union', Volume 4' (in this report referred to as 'EU GMP').

In Denmark, all finished product manufacturers must have an authorisation from the Danish Medicines Agency granted in accordance with section 39 of the Danish Medicines Act. Such authorisation can only be granted and maintained provided that the finished product manufacturer demonstrates to the Danish Medicines Agency that he is still able to meet the specific requirements applying to the pursuit of his activities.

3.2. Rules on the manufacture of APIs

The finished product manufacturer must ensure that the active pharmaceutical ingredients used as raw materials in the manufacture of medicinal products and intermediate products are manufactured in accordance with good manufacturing practice for active pharmaceutical ingredients, cf. section 10(1)(iii) of the GMP order. Detailed guidelines for good manufacturing practice for active pharmaceutical ingredients have been provided in the 'Rules Governing Medicinal Products in the European Union', Volume 4, Part II' (in this report referred to as 'EU GMP, Part II').

The API manufacturer is generally not required to have an authorisation under section 39 of the Danish Medicines Act to manufacture, repack or distribute chemical APIs in Denmark and bears no separate liability under the GMP order. The manufacture of APIs of biological origin (including classical fermentation) is, however, considered such an integrated part of the manufacture of the medicinal product that it is subject to prior authorisation being obtained by the manufacturer from the Danish Medicines Agency, cf. section 39 of the Danish Medicines Act.

Companies manufacturing APIs in Denmark are subject to inspection by the Danish Medicines Agency in accordance with section 44 of the Danish Medicines Act. The Danish Medicines Agency solely carries out inspections based on a risk assessment or at the company's request. Upon completion of the inspection, the Danish Medicines Agency issues a GMP certificate to the API manufacturer provided that the manufacturer is in satisfactory compliance with the current rules.

Companies manufacturing APIs outside of Denmark are subject to inspection by the Danish Medicines Agency in accordance with the Compilation of Community Procedures[4], published by the European Medicines Agency (EMA).

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[2] In this report, a 'finished product manufacturer' is a company which has been granted authorisation (or a GMP certificate) to manufacture medicinal products or intermediate products, irrespective of whether the company manufactures intermediate products or finished medicinal products. The designation has been chosen to make a clear distinction between these manufacturers and API manufacturers and traders.

[3] Cf. Danish executive order no. 1242 of 12 December 2005.

[4] Compilation of Community Procedures on Inspections and Exchange of Information; Guidance on the occasions when it is appropriate for competent authorities to conduct inspections at the premises of manufacturers of active substances used as starting materials.

4. Guidelines on the control and monitoring of APIs

4.1. Quality assurance and quality control of API

Finished product manufacturers must ensure that APIs are manufactured in accordance with the conditions set out in the marketing authorisation as well as in accordance with the rules set out in EU GMP, Part II. When medicinal products are manufactured in accordance with the rules set out in EU GMP, uniform processes and products are ensured. In addition, finished product manufacturers must ensure that all APIs received are of the correct quality and still meet the approved specifications.
As a manufacturer of finished products, the most efficient way of living up to his responsibility of ensuring that the purchased APIs are manufactured and distributed according to the rules set out in EU GMP, Part II, is to audit API manufacturers.
An assessment of the extent to which API manufacturers comply with EU GMP, Part II, based on submitted questionnaires, analysis results or other types of certification (such as a GMP certificate issued by an EU regulatory authority) does not provide the same level of assurance of compliance with GMP and the conditions set out in the marketing authorisation as the finished product manufacturer's in-depth knowledge of the API manufacturer.

4.1.1. Audits

When conducting an audit[5] one or more auditors visit the API manufacturer in question on behalf of the finished product manufacturer. The auditors should possess the required scientific and technical qualifications as their audit includes a review of both the API manufacturer's quality management systems, production plant and laboratories. The auditors must also have in-depth knowledge of EU GMP, Part II.
Upon completion of the audit, the auditors prepare an audit report describing which processes and procedures have been audited. In addition, the auditors prepare list of deficiencies and other comments which is submitted to the API manufacturer for written reply.
When the API manufacturer has provided a satisfactory reply to the deficiencies and comments, the auditors can prepare a conclusion and submit the complete audit report to the finished product manufacturer. Based on an evaluation of the audit report, the finished product manufacturer must decide whether the APIs in question are manufactured in accordance with good manufacturing practice for APIs.

If the API manufacturer is found to be able to ensure that the APIs in question are manufactured in accordance with EU GMP, Part II, this API manufacturer can be used as supplier of the APIs in question.
In some cases, another audit may be required before the API manufacturer can be used as a supplier. The purpose of this second audit is to ensure that all deficiencies have been handled in a satisfactory manner.

If the API manufacturer audited uses other addresses or companies (e.g. contract manufacturing sites) for part of the manufacture of APIs, such addresses or companies should also be audited.
Any repackaging sites which receive the API from the API manufacturer and repack or relabel the API before delivery to the finished product manufacturer should also be audited. In the same way as described above, auditors must also prepare reports of these audits and submit the reports to the finished product manufacturer who will evaluate whether the level of compliance with the EU GMP, Part II, is satisfactory.
In those cases where APIs must be stored under special conditions (e.g. at a temperature interval other than room temperature), it will also be relevant to audit API traders not performing manufacturing activities. The same applies if the finished product manufacturer suspects that the trader's quality management system is not sufficiently effective.

[5] In this report, 'audit' refers to the visit paid by the finished product manufacturer (or his representatives) at the API manufacturer in connection with the self-inspection programme.

The API manufacturers used and relevant traders should be audited at regular intervals to ensure that they still comply with EU GMP, Part II. An audit is generally valid for two years, but the auditing frequency should be fixed based on a risk assessment. There should, however, never be more than three years between audits carried out at the same API manufacturer.

The responsibility for the performance of audits at the required intervals and that the auditors have the necessary qualifications lies with the qualified person with the finished product manufacturer who releases the finished medicinal product to the market. By reviewing audit reports – and possibly by having participated in audits himself – the qualified person is also responsible for ensuring that API manufacturers and traders have complied with the EU GMP, Part II, during manufacture and distribution of the API.

4.1.2. Laboratory analysis

Upon receipt of the API, the finished product manufacturer conducts laboratory analysis to ensure that the API supplied still meets the approved specifications. The finished product manufacturer must (unless otherwise specified in the marketing authorisation) carry out a full control programme for each API batch in accordance with the applicable specification. Before the API received can be released for use at the finished product manufacturer, it must be ensured that the laboratory analysis results comply with the approved specifications.

5. Method

5.1. Selection for control

Overall, two different methods were used for the control performed in the project (see Figure 1):

- Laboratory control (control of documentation and analysis of APIs);
- Inspections (inspections of finished product manufacturers and API manufacturers).

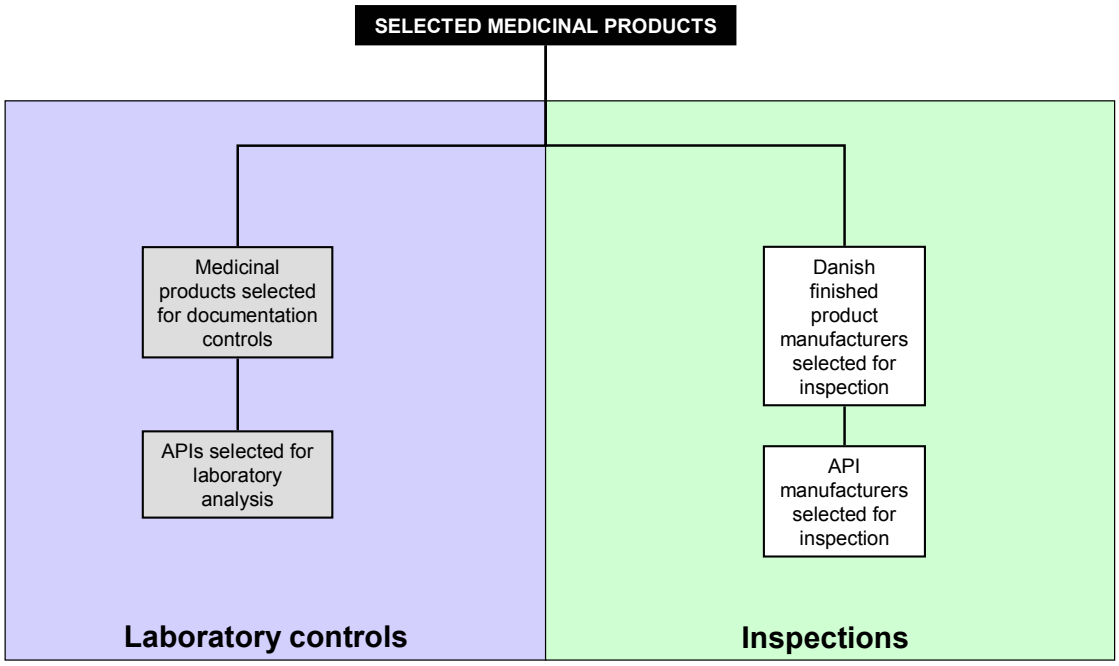

Figure 1: Selection of medicinal products for documentation control and laboratory analysis as well as finished product manufacturers for inspection.

To the extent this was practically possible, the project group based its selection of control candidates on a risk-based approach.
The project group primarily focused on methodically identifying and selecting API manufacturers which would be relevant to inspect for the Agency's medicines inspectors. Subsequently medicinal products as well as APIs for laboratory control were selected. API traders and repackaging sites were not included in the selection process.
Only medicinal products with a marketing authorisation granted by the Danish Medicines Agency were included in the survey. In addition, it was a requirement for the project group that the medicinal products were marketed at the time of selection.

5.2. First selection round

The selection of active substances[6] consisted of several separate steps. In each step, a pool of active substances was selected. Only selected active substances were included in the subsequent selection steps (i.e. with each step, the pool of selected active substances became smaller) (see Figure 2).

In step 1, the best-selling active substances (sale to Danish consumers; statistics for 2003-2007) were identified. To also ensure a certain breadth in the types of selected active substances, the selection of the best-selling active substances were deliberately distributed on

[6] In this report, 'active substance' is used as a general term for an active substance (e.g. paracetamol). It can therefore not be equalled to the designation 'API', which is used as a specific active substance from one specific API manufacturer.

the five best-selling ATC groups: C, N, A, R, G (Cardiovascular system; Nervous system; Alimentary tract and metabolism; Respiratory system; Genito urinary system and sex hormones). As a special focus area, the best-selling active substances from ATC group L (Antineoplastic and immunomodulating agents) were also selected.
For each of the ATC groups mentioned, the best-selling active substances were selected (between 2 to 5 active substances per group, depending on the quantity sold).

In step 2 of the selection process, active substances having a Ph. Eur. monograph were selected. When a monograph exists in the Ph. Eur. for a specific active substance, APIs must at all times comply with this. By only selecting active substances with monographs in the Ph. Eur., the number of different analysis methods to be set up in the Agency's laboratory was reduced.

In step 3 of the selection process, active substances were selected which were used as ingredients in at least one medicinal product with which a Danish finished product manufacturer was associated. The purpose of this was to direct the focus of the selection on medicinal products in respect of which the Danish Medicines Agency is under a special obligation to ensure that they are manufactured in accordance with existing rules.

In step 4, active substances were selected which are used as ingredients in at least one medicinal product with which an API manufacturer is associated, either located in Denmark or outside the EEA[7]. Due to the European cooperation, the Danish Medicines Agency will generally not inspect API manufacturers located in another EEA country. For that reason, medicinal products with API manufacturers located outside the EEA were of particular interest to the project group; the same applies to API manufacturers located in Denmark, as the Agency does inspect Danish API manufacturers.

In the first selection round, seven active substances had been selected for control. Twelve medicinal products were identified as containing one of the selected active substances and as relevant for the medicines inspectors to inspect (medicinal products were considered inspection relevant for the project when they met the criteria in steps 3 and 4).

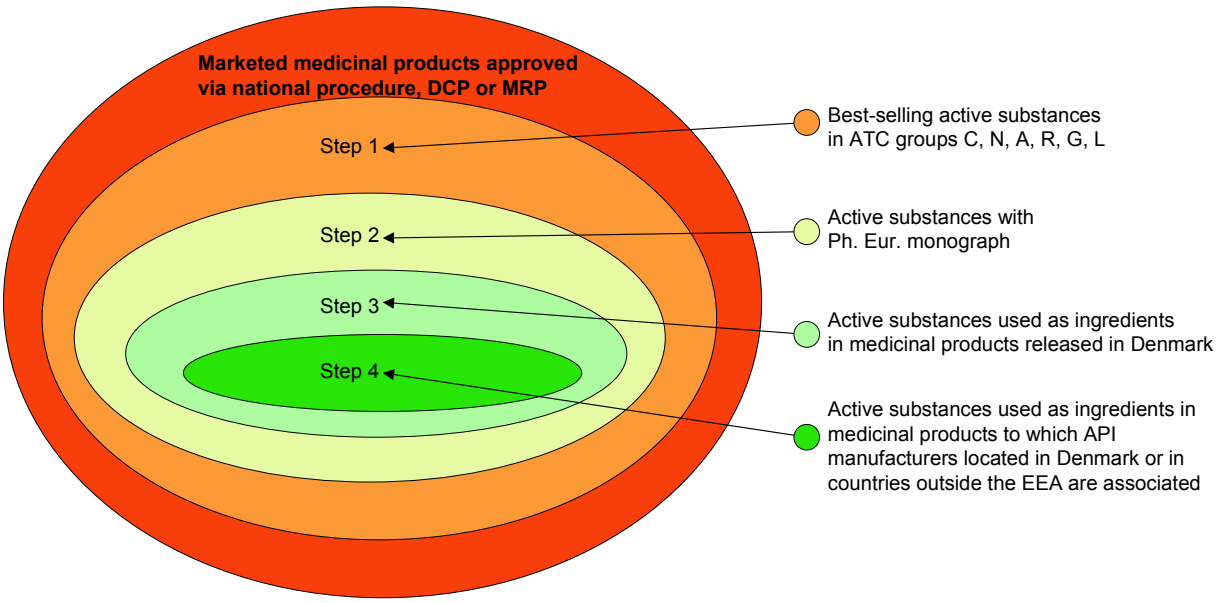

Figure 2: Selection process and criteria from the first selection round.

[7] The EEA is the European Economic Area and it consists of all EU countries as well as Norway, Liechtenstein and Iceland.

5.3. Second selection round

The goal of the project group was to select at least 15 API manufacturers for inspection. As the first selection round only identified 12 inspection-relevant medicinal products, this goal was not likely to be reached. The project group therefore carried out an additional selection round to identify more inspection-relevant medicinal products (see Figure 3).

In the second selection round, active substances were selected with complementary risk parameters compared to the first selection round, including active substances with very low sales and limited patient group.

In step 1 in the second selection round, the least selling active substances from the same six ATC groups which were used in the first selection round (C, N, A, R, G, L) were selected.

In step 2, active substances having a monograph were selected.

The criteria in steps 3 and 4 were identical to the criteria from the first selection round.

Thirteen active substances were selected in the second selection round.

In the two selection rounds, a total of 20 different active substances were selected (see Table 1).
Twenty-seven marketed medicinal products containing one of the 20 selected active substances were identified as inspection relevant (i.e. they met the criteria for steps 3 and 4).

Table 1.
Selected active substances (ATC group)

Azathioprine (L)	Medroxyprogesterone acetate (G)
Citalopram (N)	Metformin (A)
Dextropropoxyphene (N)	Sodium fluoride (A)
Diazepam (N)	Noscapine (R)
Flupentixol (N)	Phenytoinum (N)
Fluvastatin (C)	Propantheline bromide (A)
Gemfibrozil (C)	Simvastatin (C)
Gliclazide (A)	Terazosin (G)
Imipramin (N)	Tolbutamide (A)
Lamotrigine (N)	Zopiclone (N)

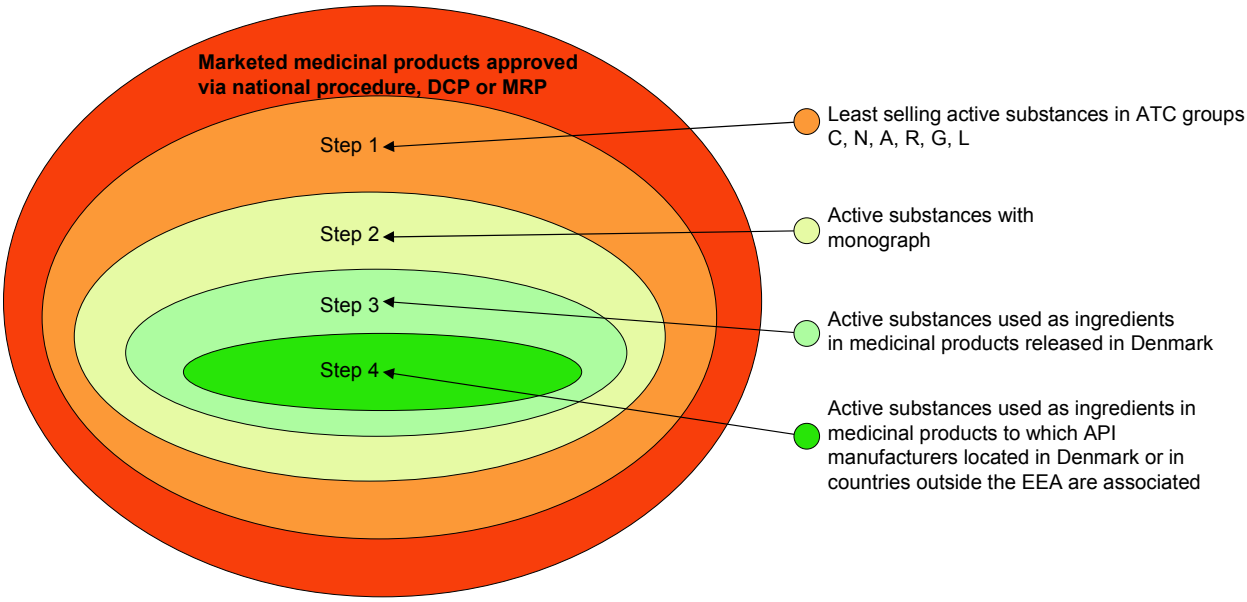

Figure 3: Selection process and criteria from the second selection round.

5.4. Selection of API manufacturers

Several API manufacturers and finished product manufacturers were associated with and approved for the majority of the inspection-relevant medicinal products. It was thus not possible for the project group to identify which companies were currently manufacturing the selected medicinal products without contacting the relevant marketing authorisation holders (MAHs).
The MAHs for the 27 inspection-relevant medicinal products were thus asked to list the API manufacturers and finished product manufacturers used in the most recent manufacture of finished products.[8]

For 15 of the inspection-relevant medicinal products, the required criteria were met; the finished product was released by a Danish manufacturer, and the API manufacturer used was located in Denmark or outside the EEA.

As several of the medicinal products contained APIs from the same API manufacturer, 12 different API manufacturers were identified who supplied APIs to the 15 selected medicinal products and were thus relevant to inspect. All 12 API manufacturers were selected for inspection.

Six of the selected API manufacturers had been inspected by a European medicines agency in 2007, 2008 or 2009. In addition, one API manufacturer had been inspected in 2006, but had stopped supplying APIs to Danish finished product manufacturers. Instead of using resources on repeating inspections of API manufacturers already inspected, inspection reports from the most recent inspections at these seven API manufacturers were obtained from the relevant regulatory authorities.

The remaining five API manufacturers were all inspected by the Danish Medicines Agency's medicines inspector in 2009 as part of the project.

5.5. Selection of Danish finished product manufacturers

Danish finished product manufacturers who received APIs from one of the 12 selected API manufacturers were also inspected by the medicines inspectors. These inspections focused solely on the monitoring by the finished product manufacturer of whether the API manufacturers used complied with the EU GMP, Part II, and that the API used was of correct quality.
In 2009, 12 Danish finished product manufacturers were inspected as part of this control.
In connection with the inspections, copies of the audit reports from audits carried out at the 12 selected API manufacturers were made available to the medicines inspectors. These audit reports were used to compare the finished product manufacturers' observations during audits of API manufacturers with the medicines inspectors own observations from inspections of the same API manufacturers.

5.6. Selection of medicinal products and APIs

A total of 82 marketed medicinal products from 37 different MAHs containing one of the 20 selected active substances were called in for control in the Agency's laboratory. For these medicinal products, the Agency requested specified documentation for the APIs and associated finished products as well as sample and reference material (see Appendix 1).

For all selected medicinal products, the laboratory carried out documentation control of the material submitted. For 41 of the medicinal products submitted, the APIs were also analysed in the Agency's laboratory for determination of ID, assay and related substances.

[8] It is possible to switch between already approved manufacturers of APIs and finished products. It must, however, be possible to trace all packages back to the actual manufacturers.

6. Results

6.1. Inspections of API manufacturers

Twelve selected API manufacturers were inspected to evaluate compliance with EU GMP, Part II. The 12 inspected API manufacturers are located in seven different countries: China, India, Mexico, Israel, Japan, the USA and Denmark.
Based on the inspections carried out, it can be concluded that all – with the exception of one manufacturer which has not supplied APIs to Denmark since 2006 – comply with the overall principles of good manufacturing practice for APIs as described in EU GMP, Part II.

The most significant or frequent deficiencies found during the inspections of API manufacturers related to the following areas:

- Lacking maintenance and cleaning of facilities.
- Lacking calibration of equipment.
- Lacking validation of process transfer and methods of analysis.

It should be mentioned, however, that there was a large difference in the level of compliance with rules among the inspected API manufacturers.

6.2. Inspections of Danish finished product manufacturers

Twelve Danish finished product manufacturers were inspected exclusively to assess the monitoring of the API manufacturers and traders used. The inspections showed that all 12 generally live up to their responsibility of ensuring that the APIs used in the manufacture of medicinal products are manufactured in accordance with EU GMP, Part II.

The most significant or frequent deficiencies found during these inspections include:

- Inadequate audit reports from audits of API manufacturers.
- Inadequate or no follow-up on deficiencies found during audits of API manufacturers.
- Missing documentation for the auditor's qualifications and independence (i.e. documentation that there is no conflict of interest between auditor and the auditee).
- Missing approval of audit reports from the qualified person with the finished product manufacturer.
- Missing audit of all relevant traders.

6.3. Comparison of audits and inspections

Copies of audit reports used by the finished product manufacturers to evaluate the level of compliance by the API manufacturers used with EU GMP, Part II, were made available to the medicines inspectors. Observations of the audit reports were subsequently compared with the medicines inspectors' own observations from the inspections of the same API manufacturers or by reading inspection reports from other European regulatory authorities.

The comparisons showed that the audit reports read did not list the same deficiencies as were observed by the medicines inspectors, and, in general, the companies' auditors listed less deficiencies than the medicines inspectors. Similarly, deficiencies were generally assigned a lower classification by auditors than by medicines inspectors.
In those cases where the audit had been performed by a third party (i.e. not by the Danish finished product manufacturer), the above-mentioned tendency was even more pronounced.

Three of the 12 audit reports reviewed offered such a misleading description of the level of compliance by API manufacturers with EU GMP, Part II, that qualified persons with the finished product manufacturers could not use these to evaluate whether the API manufacturer in question lives up to the EU GMP, Part II. In all three instances, the audit had been carried out be a third party.
In one of the above-mentioned cases, the audit report had been obtained from a European finished product manufacturer who supplied an intermediate product containing APIs from the

audited API manufacturer. In the audit report, the auditor described the API manufacturer favourably, but 15 months later the same API manufacturer was declared unsuitable for use by a European regulatory authority on the grounds of lack of compliance with rules.

6.4. Documentation control of marketed medicinal products

Control has been carried out to examine the quality of the most important parameters in the medicinal product documentation.

The review of the documentation obtained has provided the Danish Medicines Agency with comprehensive and detailed knowledge of compliance with rules from the manufacture of the API to the release of the finished product.
The following section only describes the results related to APIs.

Documentation for 77 medicinal products and related APIs were received from MAHs.
Four of the 82 medicinal products requested were deregistered by the MAHs immediately in connection with the request. In the opinion of the Danish Medicines Agency, it was thus no longer relevant to carry out the planned control of these medicinal products as a Danish marketing authorisation no longer existed. One medicinal product was deregistered immediately before a planned subsequent inspection of the finished product manufacturer, and the results of the laboratory's control of this medicinal product are thus not included in this report.

In the letters of request, a submission deadline of at least 30 days was given.
The average delivery time for the material requested was 76 days. For 46% of the controls in the project, the delivery time exceeded 76 days, of which 31% were under way for more than 100 days.

Documentation control was carried out for a total of 79 API batches. This figure exceeds the number of medicinal products received, as more API batches can be used in the same finished product batch.

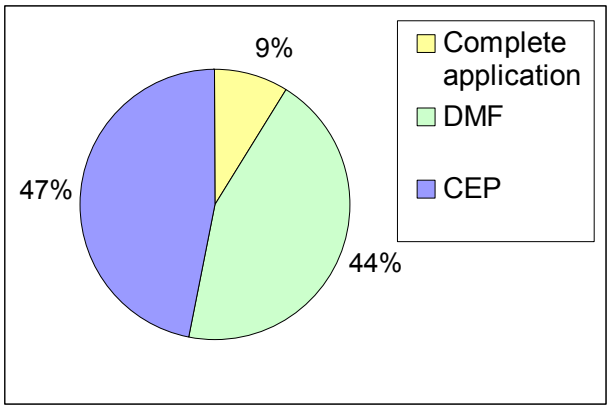

Figure 4: Distribution of types of documentation forming the basis of approval of the APIs for the medicinal products controlled in the project.

In those instances where registration documentation for APIs exists in the form of a Drug Master File (44% of the controls) or a complete application (9% of the controls), it was, due to the time factor, not examined whether there are more quality requirements than those directly set out in specifications and certificates of analysis. Where the API manufacturer has a CEP[9] (47% of the controls), additional quality requirements (e.g. re-test period, residual solvents or particle size) will explicitly appear from the CEP (see Figure 4 for a graphic distribution of documentation types).

[9] A CEP (Certificate of Suitability of the European Pharmacopoeia) is issued directly to the API manufacturers and is valid from the day of issue. A CEP may include additional requirements for an API than the applicable monograph. The requirements may depend on the API manufacturer. Often, the requirements will relate to residual solvents, but they may also relate to methods which differ from the monograph. The CEP will often include requirements for the re-test period.

In its review of the API documentation, the Agency identified different types of errors. The errors were divided into three categories (see Figure 5):

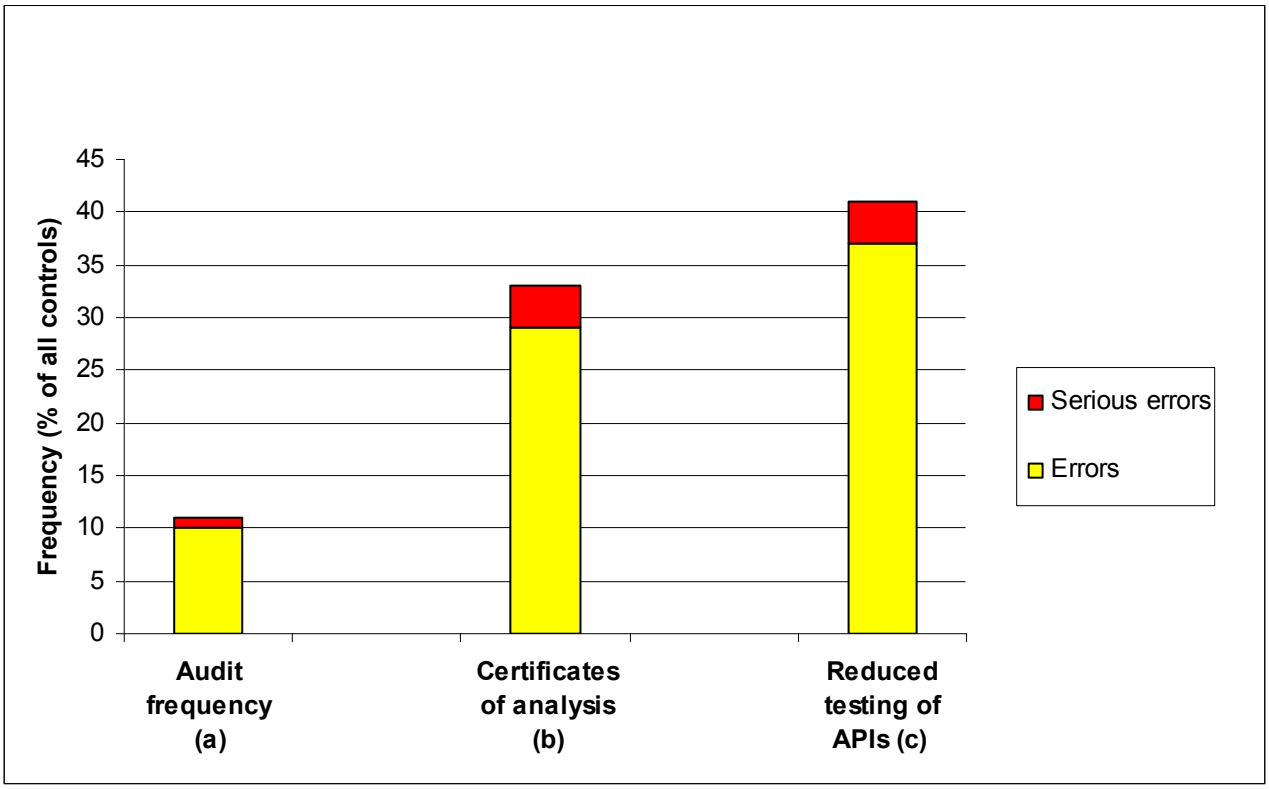

Figure 5: Errors identified during the review of 79 API documentation controls.
(a) Audit frequency: Controls in which API manufacturers were audited at a lower frequency than recommended.
(b) Certificates of analysis: Controls with errors or defects in certificates of analysis.
(c) Reduced testing of APIs: Controls in which reduced testing was used of APIs at the finished product manufacturer without this having been approved.

6.4.1. Audit frequency

In its letter of request for documentation, the Agency asked for information about the time and result of the most recent audit of the API manufacturer.
In 10% of the controls, it had been more than three years since the last audit of the API manufacturer by the finished product manufacturer. In 1% of the controls, the finished product manufacturer had never audited the API manufacturer; the Agency considers this a serious error.

6.4.2. Certificates of analysis

Certificates of analysis for APIs from the API manufacturer and the finished product manufacturer, respectively, were evaluated in connection with the control.

In 29% of the controls, the Agency observed errors and defects in respect of the certificates of analysis, e.g.:

- Missing signature or dating
- Missing re-test date, or re-test interval that differs from the DMF or the CEP
- Results listed as 'conforms' even though it is possible to specify a numerical result.

In 4% of the controls, the Agency observed acceptance limits for assay or related substances that were wider than stated in the specification. This is considered a serious error.

No results in the certificates of analysis submitted deviated from the specifications submitted.

6.4.3. Reduced testing of APIs

During the project, the Danish Medicines Agency observed that it is very different how a finished product manufacturer seeks to ensure that the API used meets the specification requirements. It varies from a complete test of the specifications at the finished product manufacturer to a complete transfer of analysis results from the API manufacturer's certificate of analysis to the finished product manufacturer's certificate of analysis for the API.
In connection with the controls, no MAH submitted documentation that the use of reduced testing had been applied for and approved by the Danish Medicines Agency.

In 37% of the controls, the complete analysis of the API had not been conducted at the finished product manufacturer.

In 4% of the controls, all analysis results for the API had been transferred from the API manufacturer's certificate of analysis to the finished product manufacturer's certificate of analysis without noting this on the certificate. This is considered a serious error.

It is only noted explicitly on a few certificates of analysis that the results in question are transferred from the API manufacturer.

6.4.4. Other observations

In this project, some of the companies had difficulties procuring the requested material. MAHs which are both manufacturers of APIs and finished products did, however, often submit material of a high quality.

- In 20% of the controls, the API had been analysed using an in-house method (and thus not a Ph. Eur. method).
- In approx. 10% of the controls, the specification' version number did not correspond to the certificate of analysis's specification reference (i.e. specifications had been changed by the API manufacturer or the finished product manufacturer without having been approved by the Danish Medicines Agency).
- In 5% of the controls, an insufficient quantity of the API had been retained to accommodate the Agency's request.
- In 5% of the controls, the flow chart of companies used for analysis did not specify which control laboratories had been used.

6.5. Laboratory analysis

The Danish Medicines Agency requested a number of samples of APIs, finished products and reference substances to be able to carry out selected analysis of the APIs. It was essential that finished products were available in order to follow the API's way to the consumer, including to investigate whether any quality problems in relation to the API are carried over to the finished product.

So far, the laboratory has analysed 46 API batches distributed on six active substances. All the methods used were described in the European Pharmacopoeia. Analysis has been performed to determine ID, assay and related substances.

In connection with this project, laboratory control was carried out for the following active substances: Simvastatin (15 batches), lamotrigine (11 batches), citalopram (8 batches), gliclazide (6 batches), medroxyprogesterone acetate (5 batches) and noscapine (1 batch).

In four citalopram batches, the Agency's laboratory found a level of unspecified related substances which was significantly higher than the limit allowed in the monograph. In one of these batches, two unspecified related substances were found which were above the allowed limit stated in the monograph.

In one gliclazide batch, the Agency’s laboratory found an unspecified related substance content which was higher than the specification limits.

7. Discussion

The most frequent or significant observations made by medicines inspectors and the Agency's laboratory have been compared and are discussed below.

7.1. Inadequate audit reports from audits of API manufacturers

An audit conducted before qualification of a new API manufacturer should cover all relevant processes related to the manufacture and handling of the API used.
In subsequent audits of the API manufacturer, it is natural not to focus on the same areas as those focused on in the previous audit. An audit report is thus not expected to describe all processes relevant to the API in question. Auditors should instead focus on areas which have not been audited recently or which have previously proved a challenge for the API manufacturer.

As the qualified person with the finished product manufacturer uses audit reports to evaluate the level of compliance by the API manufacturers and traders used with EU GMP, Part II, audit reports must explicitly describe which areas the audit has covered.

In connection with the project, it was observed that audit reports requested from Danish finished product manufacturers were inadequate.

Only by explicitly describing which areas an audit has concerned can subsequent audits be targeted at areas not previously audited.

The qualified person who uses audit reports to evaluate the level of compliance by the API manufacturer with EU GMP, Part II, must have access to all previous audit reports to obtain a satisfactory overview.

7.2. Inadequate or no follow-up on deficiencies found during audits of API manufacturers

Deficiencies found at the API manufacturer during audits are handled by the API manufacturer and they should provide the auditor with a reply in due time. If the auditor or the qualified person with the finished product manufacturer finds it necessary, a follow-up audit should be carried out when the API manufacturer has reported back, so that there is no doubt that the deficiencies have been dealt with in a satisfactory manner.
In their review of audit reports, the medicines inspectors observed that it took up to a year to provide a reply to and close deficiencies after the latest audit, and, in some cases, they observed that deficiencies found more than a year ago still had not been handled.

Deficiencies not closed in a satisfactory manner should not be ignored by neither the auditor nor the qualified person with the finished product manufacturer. In an audit carried out before qualification of a new API manufacturer, all deficiencies should be closed before APIs from the API manufacturer in question are used. Similarly, the finished product manufacturer should, based on a risk assessment, decide whether he will continue using an already qualified API manufacturer if the API manufacturer is unable to provide a satisfactory reply to deficiencies.

7.3. Missing documentation for the auditor's qualifications and independence

The auditors' qualifications (including third party auditors) must be evaluated and documented by the finished product manufacturer. It must also be ensured that the auditor is independent (i.e. documentation that there is no conflict of interest between auditor and the auditee).

During inspections of finished product manufacturers, medicines inspectors observed that neither CVs for auditors nor documentation for training could be produced.

Qualification of API manufacturers via audits is the responsibility of the qualified person. If the qualified person delegates this task to others (internally in the company or externally), the

qualified person is responsible for ensuring that the auditor selected has the required qualifications, both in terms of training, experience, education and personal characteristics.

If a finished product manufacturer only purchases small quantities of API from an API manufacturer, it may sometimes be difficult to be allowed to carry out a sufficiently thorough audit. It may thus be advantageous to either acquire an audit report from an audit already performed or to collaborate with other manufacturers of finished products who also want to audit the API manufacturer in question.

It was observed that audit reports prepared by a third party (i.e. not the finished product manufacturer himself) are generally more favourable than those prepared by the finished product manufacturer himself.

When requesting third-party audit reports, finished product manufacturers must, in particular, focus on the auditors being sufficiently qualified and independent of the audited API manufacturers. Special caution should be exercised when using auditors affiliated with traders or finished product manufacturers supplying APIs, intermediate products or finished products to other companies.

7.4. Missing approval of audit reports from the qualified person with the finished product manufacturer

The finished product manufacturer must carry out a documented evaluation of the audit of the API manufacturer which evaluates whether the API manufacturer is in satisfactory compliance with the requirements set out in EU GMP, Part II, and the conditions set out in the marketing authorisation.

During inspections at finished product manufacturers, the medicines inspectors observed that neither the qualified person nor other QA employees had acknowledged having read and evaluated audit reports from audits of API manufacturers.

If the qualified person does not perform the above-mentioned task himself, he must have a system in place to ensure that qualified employees perform the evaluation on behalf of the qualified person.
If audit reports are not evaluated, there is a risk that the auditor has ignored important processes or procedures in his audit, and that the audit has not been sufficiently thorough to provide a true and fair view of the conditions at the API manufacturer.

7.5. Missing audit of all relevant suppliers

Finished product manufacturers should have audit reports for all API manufacturers used. If the API manufacturer audited uses other addresses or companies (contract manufacturing sites) for part of the manufacture of APIs, such addresses or companies should also be audited. The same applies to any suppliers who repack, relabel or analyse the API.

During the project, the medicines inspectors noted that not all relevant traders had been audited. This increases the risk of non-compliance of either the manufacturing conditions or the storage conditions with the requirements which are approved in the marketing authorisation and described EU GMP, Part II. Missing audits of all links in the supply chain also increases the risk that APIs are handled by companies whose quality management systems do not effectively minimise the risk of counterfeit APIs being introduced in the supply chain.

7.6. Lower frequency of audits of API manufacturers than recommended

After two years, an audit report cannot be expected to provide a true and fair view of the conditions at the audited API manufacturer. Audits should, as a minimum, be carried out every three years, even if a medicines agency has carried out an inspection in the meantime.
An inspection report from an EU medicines agency cannot replace an audit, but the report can be used to postpone an audit. Similarly, previous audits showing positive results as well as extensive experience with the API manufacturer may speak in favour of audit intervals of more than two years.

Of the medicinal products requested by the Agency's laboratory, 11% contained APIs from API manufacturers that had not been audited on behalf of the finished product manufacturer within the past three years. A low audit frequency increases the risk of GMP non-compliance by API manufacturers.

The qualified person with the finished product manufacturer who released the finished medicinal product to the market is responsible for ensuring that API manufacturers and relevant traders are audited at the recommended frequency.

7.7. Audit reports not comparable with medicines inspectors' observations

In connection with the inspections of Danish finished product manufacturers, the medicines inspectors received copies of relevant audit reports. These audit reports were used to compare the companies' observations during audits of API manufacturers with the medicines inspectors own observations from inspections of the same API manufacturers.
The audit reports and inspection reports were not prepared at the same time, i.e. the audits and the inspections were not carried out simultaneously. In some cases, the inspection was carried out before the audit, and in other cases it was the other way round. It is thus difficult to conclude that the two reports describe exactly the same situation, as certain changes in processes, systems and quality level at the API manufacturers must be expected over time. In the opinion of the Danish Medicines Agency, the quality level at API manufacturers do, however, rarely deteriorate. This means that if an audit report describes an API manufacturer as having a high quality level this should normally not have changed significantly if an inspection is subsequently carried out at the same address.

The audit reports generally noted a lower number of deficiencies than the inspection reports. In addition, these deficiencies were classified as less critical in the audit reports than in the inspection reports. Three audit reports were qualitatively and quantitatively inadequate to such an extent that they did not provide a true and fair view of the conditions at the API manufacturer.
When considering that auditors and qualified persons are facing a challenging task when trying to identify whether deliberate cheating takes place at API manufacturers or other links in the supply chain, misleading audit reports pose a serious problem.

If the qualified person with the finished product manufacturer has not participated in or carried out the audit of the API manufacturers used, audit reports are by far the best tool for the qualified person to evaluate the conditions at the API manufacturers. It is thus essential that all recommendations and deficiencies are noted in the audit reports, and that deficiencies are classified in accordance with a generally accepted principle.

It should be noted that the medicines inspectors experienced that not all finished product manufacturers were aware that audit reports must be made available to the medicines inspector upon request. The reason for the confusion was that in some audit reports it was stated that they were not to be made available to any third parties. The Danish Medicines Agency expects that audit reports can be made available to the Agency as required[10]. Finished

[10] cf. section 44(2)(ii) of the Danish Medicines Act.

product manufacturers must thus ensure that they, when purchasing audit reports from consultancy firms, do not agree that the reports may not be shown to the relevant authorities.

7.8. Lack of action from MAHs on withdrawn CEP

MAHs should regularly keep themselves updated on the status of the CEPs which are authorised under the marketing authorisation.

In connection with the project, it was observed that an API manufacturer whose CEP had been withdrawn due to lack of GMP compliance, had not been removed from the relevant marketing authorisation.

If the Directorate for the Quality of Medicines & Healthcare (EDQM) withdraws or suspends a CEP, the Danish Medicines Agency expects that the MAH will take the necessary measures to ensure that the use of APIs from the API manufacturer in question is discontinued permanently or for a period of time. When the CEP of an API manufacturer is withdrawn or suspended, it must, based on a risk assessment, be decided whether the API batches from the API manufacturer in question must be withdrawn from the market. The MAH must also as soon as possible submit a variation application which removes the API manufacturer in question from the relevant marketing authorisations.
CEP suspension and withdrawal is published at EDQM's website (www.edqm.eu).

7.9. Reduced testing of APIs

In addition to the ongoing control that API manufacturers comply with EU GMP, Part II, laboratory analysis of the APIs received also play an important role in ensuring that the APIs have the required quality and composition.
The project observed several instances of results from an API manufacturer's certificate of analysis having been transferred to the finished product manufacturer's certificate of analysis, i.e. without the finished product manufacturer having repeated the analysis.

Such use of reduced testing must be authorised by the Danish Medicines Agency and be described in the marketing authorisation, cf. section 26(1) of the Danish Medicines Act.

If either the MAH or the finished product manufacturer wants to lower or change the agreed test frequency, an updated API specification must be submitted. This is a change of the MAH's registration documentation, and a variation must therefore be applied for. Thus to have the use of reduced testing approved, it does not suffice that the finished product manufacturer during an inspection by the Danish Medicines Agency agrees with the medicines inspector that the use of reduced testing is acceptable.

The Danish Medicines Agency is aware that the above mentioned requirement has not systematically been enforced. The Agency will initiate an international discussion about the requirement.

7.10. Use of monograph and in-house methods

From an analysis point of view, the requested APIs range from older, well-known active substances to relatively new – less tested – active substances. This is reflected in whether the individual active substances are included in the European Pharmacopoeia and, for the substances included, when the first standard entered into force. Some monographs for the requested APIs have thus been included in the Pharmacopoeia for years, while others were published in 2009.

When 20% of the requested APIs were tested using in-house methods at the finished product manufacturer, it should be seen in the light of the time of publication of the relevant monographs.

Citalopram and lamotrigine were both published in Supplement 6.3 to the Ph. Eur. – valid from January 2009. Fluvastatin was published in Supplement 6.4 to the Ph. Eur. – valid from 1 April 2009.
Batches from these three active substances were tested by the finished product manufacturers using methods that differed from those described in the European Pharmacopoeia, as the manufacture of the APIs took place before the monographs entered into force.
Four batches were tested by the finished product manufacturer using in-house methods at a time when the monographs in the European Pharmacopoeia were valid. It should be pointed out that the valid monographs in the European Pharmacopoeia must be used unless another method has been approved by the competent authorities.

A single API (terazosin) was tested using an in-house method as the finished product manufacturer did not find the valid Pharmacopoeia method applicable. When applying the Pharmacopoeia method, it was not possible to determine the individual related substances correctly, which also appears from the knowledge database in the terazosin monograph.
If a company experiences that Ph. Eur. monographs do not work as intended, this should be communicated to the EDQM or the Danish Medicines Agency.

7.11. The registration department and the QC department do not work with synchronised specifications

Specifications should always be updated in the following three places:

- The MAH's registration department;
- The finished product manufacturer's QC department;
- The Danish Medicines Agency's dossier on the product.

In approx. 10% of the controls, the specifications from the MAH's registration department differed from those in the finished product manufacturer's QC department.
In most of the above cases, specifications were submitted which were similar to those having been approved in the initial registration application. In the cases in question, these specifications have apparently been changed subsequently by the manufacturer's QC department without having notified the MAH and without having submitted a variation application to the Danish Medicines Agency.

Such lack of dialogue between the MAH and the manufacturer means that any changed specifications are not communicated between the registration department and the QC department, and that the QA department thus releases finished medicinal products or APIs based on non-approved specification limits.

7.12. Uncertainty about reference samples

In connection with the request for APIs, some companies were not able to deliver the requested quantity to the Agency. The Agency requested 5 g of API which is the estimated quantity to be used for a complete monograph analysis. According to the rules[11], a quantity should be retained corresponding to two complete analysis, i.e. all analysis comprised by the specification.

The primary purpose of retaining samples is to enable the MAH or the finished product manufacturer to perform future quality analysis if the quality of the API is questioned. It is also the purpose to meet the authorities' request for samples for analysis. The retained sample quantity at the finished product manufacturer should be adjusted to these considerations.

[11] Cf. Annex 19 of the EU GMP.

7.13. Results of the Danish Medicines Agency's laboratory analysis

The Danish Medicines Agency requested a number of samples of both APIs, finished products and reference substances to be able to carry out selected analysis of the APIs. It was essential that both APIs and finished products were available in order to follow the API's way to the patient, including to investigate whether any problems with quality in relation to the API are carried over to the finished product.

During the project, in connection with the submission of samples, several instances were observed of material which required special storage conditions. The Danish Medicines Agency received material which had not been submitted in accordance with the correct storage conditions. It is not possible to decide how long the submitted material had been stored incorrectly.

Four citalopram batches contained a level of unspecified related substances which was significantly higher than the limit stated in the monograph.
All four batches were manufactured before the implementation of the monograph and were thus released by the API manufacturer based on in-house specifications where detection did not take place at the same wavelength as described in the monograph.
At the time of the Agency's control one of these four batches had exceeded its re-test date.
The Agency is in ongoing dialogue with MAHs on how to handle the observations.

Three gliclazide batches had a content of an unspecified related substance which was 4-5 times higher than the content specified in the certificates of analysis for these batches. The content of unspecified related substances observed was, however, within the approved specifications.
The Danish Medicines Agency has decided to investigate these differences in analysis results in more detail and has via the MAH requested chromatographic raw data from both the API manufacturer and the finished product manufacturer. In addition, the Agency has asked the MAH to provide more details as to whether the related substance in question originates from synthesis or degradation.
The difference in analysis results cannot be explained by studies of these data, and the difference must be ascribed to originate from gliclazide degradation.

8. Conclusion

The purpose of the project was to improve the basis for pharmaceutical companies' control of API manufacturers and traders. In the opinion of the Danish Medicines Agency, the existing legislation effectively ensures that finished product manufacturers use APIs of a high quality. Finished product manufacturers and marketing authorisation holders generally work according to the rules governing the area. The Agency has, however, identified the following areas with room for improvement:

- The quality of audits and audit reports should be improved for audits of both API manufacturers and traders.
- More attention should be paid to analytical control of the used APIs by both finished product manufacturers and marketing authorisation holders.
- Withdrawal of CEPs should always result in a risk assessment by both the finished product manufacturer and the marketing authorisation holder.

Based on the observations made in the project, the Danish Medicines Agency will prepare guidelines for the finished product manufacturers' auditors for use in connection with the preparation of audit reports.
In addition, the Agency will provide advice on the role of the qualified person, in particular in relation to APIs and API manufacturers, in connection with the release of finished products.

The project has illustrated that effective control of APIs and API manufacturers requires close dialogue between pharmaceutical companies and regulatory authorities.
The Danish Medicines Agency will maintain this close dialogue and will also in future expand our experience base for the benefit of patient safety.

9. Definition of terms

Term	Meaning	Explanation
API	Active Pharmaceutical Ingredient	Used in this report for specific active pharmaceutical ingredients from specific manufacturers and not as a general term (see 'Active substance')
ATC	Anatomical Therapeutic Chemical Classification System	
Audit		Visit paid by the finished product manufacturer (or his representative) at an API manufacturer to control his quality management system and production plant. Is carried out by companies (can in this report be equalled to 'self-inspection').
CEP	Certificate of Suitability of the European Pharmacopoeia	Certificate issued by the EDQM.
DCP	Decentralised Procedure	
DMF	Drug Master File	All documentation related to the manufacture and quality of an API. Can in this report be equalled to the Active Substance Master File (ASMF).
EDQM	European Directorate for the Quality of Medicines & Healthcare	
EMA	European Medicines Agency	
EU GMP		Is in this report used for the 'Rules Governing Medicinal Products in the European Union, Volume 4'.
Finished product manufacturer		Is in this report used for all manufacturers of intermediate products or finished medicinal products (i.e. all manufacturers with the exception of API manufacturers).
GMP	Good Manufacturing Practice	
Inspection		Visit paid by a medicines inspector at the medicinal product manufacturer to check compliance with rules. Is carried out by medicines agencies and should thus not be mistaken for 'audit' which is carried out by companies.
Active substance		Used in this report as a general term for an active substance. It can therefore not be equalled to the designation 'API', which is used as a specific active substance from one specific manufacturer.
MAH	Marketing Authorisation Holder	
MRP	Mutual Recognition Procedure	
Ph. Eur.		The European Pharmacopoeia.
QA	Quality Assurance	
QC	Quality Control	

10. Appendix 1

Danish Medicines Agency

DOCUMENTATION AND SAMPLES REQUESTED FOR TESTING *

*cf. Danish Medicinal Products Act, Section 44 (2).

Danish Medicines Agency **Journal No**	
Medicinal Product (name, pharmaceutical dosage form and strength)	
Marketing authorisation holder (and Danish representative if any)	

Annex No.	API	Requested	Company signature
1.	Certificate of Suitability of the European Pharmacopoeia (CEP), if existing.	X	
2.	Name and address of the manufacturer(s) Reference to Drug master File number (DFM is not to be forwarded)	X	
3.	From the manufacturer of the active substance: Certificates of analysis from the last 5 batches of the active substance used in the manufacturing of the medicinal product released to the Danish Marked. The specification for the API is also requested.	X	
4.	Name and address of the company(ies) responsible for batch release in EEA.	X	
5.	API batch release analytical procedures, in sufficient details enabling the procedures, to be repeated in our laboratory. Including type chromatograms, list of buffers, columns and chemicals used.	X	
6.	Certificates of analysis from the release of the last 5 batches of the API used in the finished product released to the Danish Marked.	X	
7.	Date and result of the last audit of the API manufacturer(s) performed by the responsible company.	X	
8.	If the API manufacturer has been inspected by a European authority; an EU-GMP certificate issued by the relevant inspectorate.	X	

Annex No.	Finished Product	Requested	Company signature
9.	A flow-chart indicating the sequence and activities of the different sites involved in the manufacturing of the finished product (including batch control sites) should be provided for each of the 5 batches. All manufacturing sites involved in the manufacturing process of each source of active substance, including quality control/in-process testing sites, should be listed. (Brokers or supplier detail alone are not acceptable).	X	
10.	Current release and shelf-life specification and corresponding date of approval by the Danish Medicines Agency	X	
11.	Updated analytical procedures in sufficient details enabling the procedures to be repeated in our laboratory, including type chromatograms and list of buffers and chemicals used. Date of approval of the actual methods by the Danish Medicines Agency. *Note: If the procedures refer to other documents which are necessary for correct performance of the procedure or evaluation of the results, these documents should also be provided.*	X	
12.	Validation reports for all relevant analytical methods, e.g. Assay, dissolution and related substances	X	
13.	A review of changes (a list) in specifications for the finished product since first Marketing authorisation for the Danish marked was granted.	X	
14.	Certificate of analysis for the forwarded batch and for the last 5 consecutive batches produced for the Danish marked.	X	
15.	Certificate of analysis for the In-house Reference substances (secondary standard) if used. In addition documentation concerning the traceability to an official primary standard should be provided.	X	
16.	Impurities, according to analytical procedures* Sufficient amount for 5 weight outs	X	
17.	Traceable certificates of analysis for the impurities (if available).	X	
18.	Reagents (used in the analytical procedures) if not commercially available.	X	
19.	Safety Data sheets (if relevant)	X	

** If official Reference Substances as EP-CRS or BP-CRS are used instead of In-house References Substances these should be provided*

Date *Signature*