An Integrated Solution for Calculating Results from Tests for Content Uniformity of Dosage Units According to the United States and European Pharmacopeia

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INTRODUCTION

In January 2007 the United States Pharmacopeia issued a revision of general chapter <905> that provides details on how to perform uniformity of dosage units experiments.[1] This revision covers procedures for running experiments and for assessing the data. In particular, the revised procedures for assessing the data are more complex. The revised procedure of content uniformity testing for common dosage forms in USP is almost identical to the procedure in the European Pharmacopeia,[2] but the USP has different requirements for special dosage forms, such as suppositories, transdermal patches, and premetered inhalants.

To ensure the consistency of dosage units, each unit in a batch should have an active substance content within a narrow range of the amount claimed on the label. The content uniformity test is often performed with HPLC. In many labs the chromatographic results are frequently copied into spreadsheets in order to perform the calculations. This process can be time consuming and transcription errors are a common problem.

In addition, data from two different experiments must often be compared, as the content uniformity test procedure can involve two different experimental stages. For example, if the first 10 units tested do not fulfill the requirements, 20 additional units must be tested and the total of 30 units must be evaluated. Every stage has its own specific pass/fail criteria.

Three different cases for different dosage forms and pharmacopeias, respectively, must be distinguished (Table 1).

Table 1. Acceptance Criteria			
Stage	**EP and USP common dosage forms[1]**	**USP suppositories**	**USP transdermal systems and inhalations packaged in premetered dosage units**
1 (n=10)	Acceptance value ≤ maximum allowed acceptance value L1 (L1 is 15.0 by default.)	No unit outside 85.0–115.0% of the label claim[2] and RSD ≤ 6.0%	No unit outside 75.0–125.0% of the label claim,[2] not more than one unit outside 85.0-115.0% of the label claim[2] and RSD ≤ 6.0%
2 (n=30)	Final acceptance value ≤ L1 and no individual content of any dosage is less than (1-0.01*L2)*M nor more than (1+0.01*L2)*M (L2 is the maximum allowed range for deviation of each dosage unit from the reference value and is 25.0 by default.)	No unit outside 75.0–125.0% of the label claim,[2] not more than 1 of 30 units outside 85.0–115.0% of the label claim[2] and RSD of the 30 units ≤ 7.8%	No unit outside 75.0–125.0% of the label claim,[2] not more than 3 of 30 units outside 85.0–115.0% of the label claim[2] and RSD of the 30 units ≤7.8%

[1]Common dosage forms include: uncoated, coated, or molded tablets; capsules; oral solutions in unit-dose containers; suspensions, emulsions, or gels in single-unit containers (that are intended for systemic administration only); and solids (including sterile solids) in single-unit containers.

[2]Dependent on the average of the limits specified in the potency definition in the individual monograph and mean value of the results, "label claim" is replaced by "label claim multiplied by the average of the limits specified in the potency definition in the individual monograph divided by 100" or by "label claim multiplied by the average value of the units tested (expressed as a percent of label claim) divided by 100".

The Chromeleon® Chromatography Management Software (CMS) incorporates advanced features that allow easy calculation of all the content uniformity test results. In addition, the built-in query function allows the creation of a content uniformity report that summarizes the results of two different content uniformity experiments in a single document.

This new content uniformity functionality will speed up the calculation and reporting process, reduce user errors, and provide a convenient method for reporting content uniformity data quickly.

DATA IDENTIFICATION

When performing content uniformity experiments, large amounts of chromatographic data are created, especially when two stages are executed. Workflow is often easier if samples from more than one content uniformity experiment are included in one sequence. If a drug fails the Stage 1 test, the Stage 2 samples may be run in a separate sequence, yet still have to be evaluated with the results from the first stage. Therefore it is very important to identify uniquely the data from different experiments, to facilitate searching and reporting.

All this is achieved through the use of the “User-Defined-Column” function that is available in Chromeleon. For the content uniformity test, a set of user defined columns is created in the sequence (Figure 1). The User Defined Columns (UDC) “CUT_No” and “Test_Stage” are used to identify the required data.

A

B

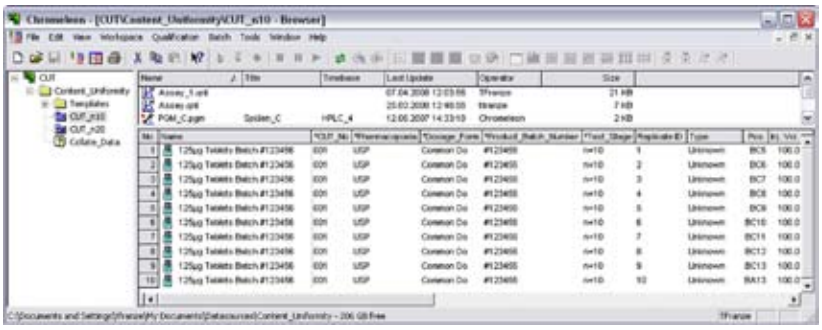


Figure 1. User Defined Columns for identification of required data.

The column “CUT_No” displays a user-defined identification of the content uniformity test experiment and offers the user an input field without limitations, allowing the use of internal numbers or codes. The column “Test_Stage” offers the user a drop down list to indicate which stage of the content uniformity experiment is performed with this sample. Available options are stage n = 10 and stage n = 30.

DATA ENTRY FOR CALCULATIONS AND PLOTTING

To be able to calculate all content uniformity results and to create content uniformity plots, additional information is required (Table 2).

Table 2. Additional Information Required

Field	Description	Location
Pharmacopeia	Choice between EP and USP	Sequence
Dosage_Form	Groups as defined in the USP	Sequence
Product_Batch_Number	Name for the tested batch	Sequence
CUT_No	Number of the experiment	Sequence
Test_Stage	n=10 or n=30	Sequence
L1	Maximum allowed acceptance value	Quantification Method
L2	Maximum allowed range for deviation of each dosage unit tested from the Reference value	Quantification Method
Correction_Factor	Correction factor if analytical methods for assay and content uniformity testing are different	Quantification Method
Target_Content	Target content per dosage unit at time of manufacture expressed as a percentage of the label claim	Quantification Method
dp_Target_Content	Number of decimal points for target content	Quantification Method
Report_Peak	Defines the peak to report	Quantification Method

Analogous to the data identification, User Defined Columns are used to create entry fields for the additional information necessary. If the information is sample specific, the UDCs are created in the sequence (Figure 1 and Table 2). If the information is peak specific, the UDCs are created in the quantification method (Figure 2 and Table 2).

No.	Peak Name	Ret.Time	Standard	Cal.Type	Peak Type	*L1	*L2	*Correction_Factor	*Target_Content	*dp_Target_Content	*Report_Peak
1	Test Substance	11.767 min	External	LOff	Auto	15.0	25.0	1.050	102.0	1	1st
2	Peak 2	15.000 min	External	LOff	Auto	15.0	25.0	1.050	102.0	1	2nd
3	Peak 3	17.000 min	External	LOff	Auto	15.0	25.0	1.050	102.0	1	3rd

Figure 2. User Defined Columns in the quantification method.

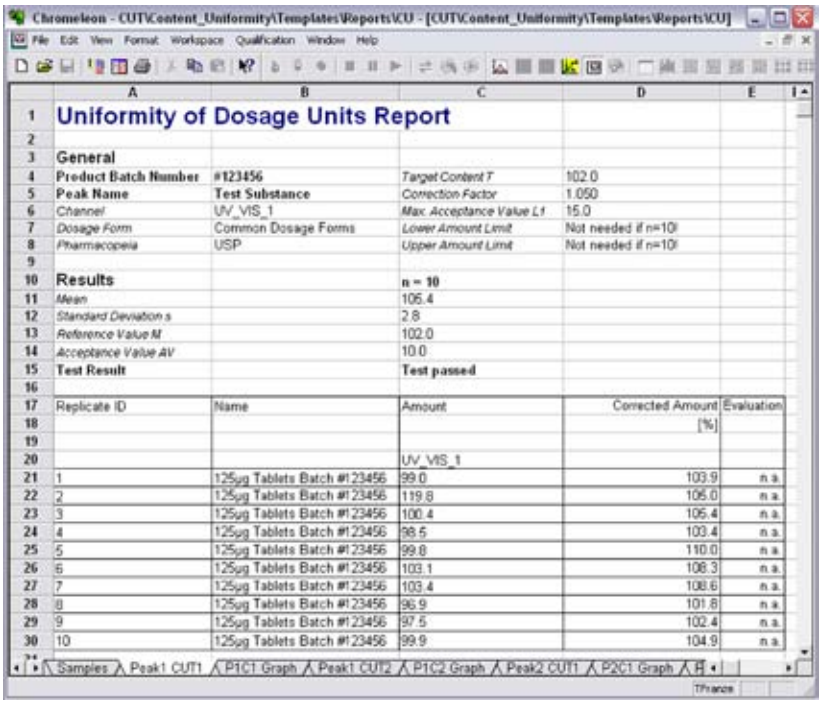
One report is used for content uniformity testing according to the European Pharmacopeia and "common" dosage forms according to the United States Pharmacopeia. The second report is used for Suppositories, Transdermal Systems, and Inhalations Packaged in Premetered Dosage Units tested according to the USP. The content of the UDCs "Dosage_Form" and "Pharmacopeia" determines which report to use. While one report is valid, the other one automatically gets invalid and a warning that this sheet is invalid is displayed. Three analogous reports are available in parallel for reporting up to three different active substances in multi-drug products.

RESULT CALCULATION

Chromeleon provides all standard chromatographic calculation tools, such as amount, statistical calculations (e.g. average, standard deviation and relative standard deviation), and advanced spreadsheet formulas. These calculations can be applied to any user-defined data set.

Case 1: United States Pharmacopeia for common dosage forms and European Pharmacopeia

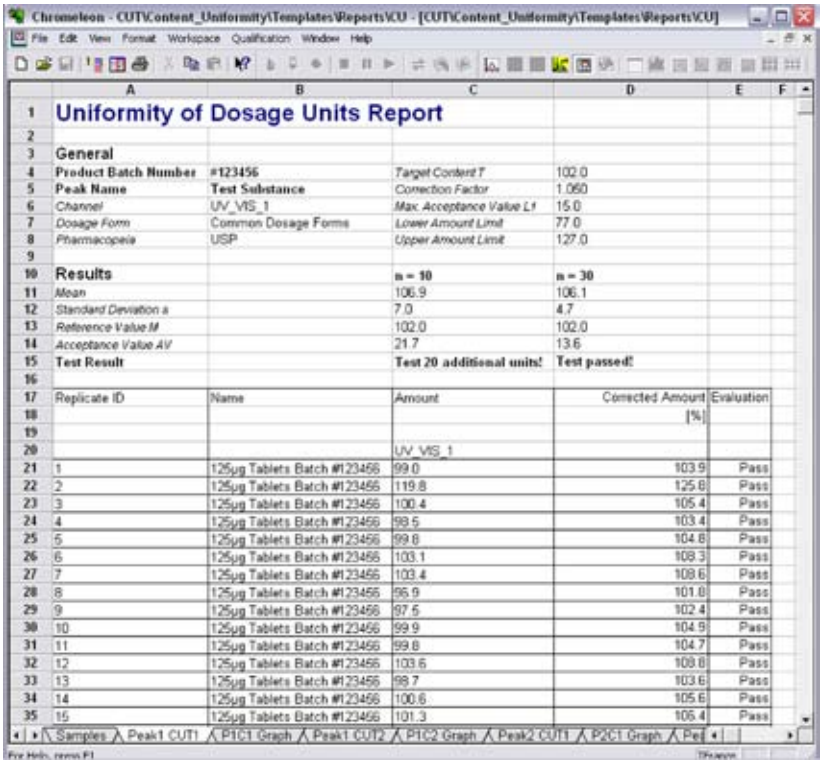
Stage 1 of the content uniformity test starts with 10 dosage units. An acceptance value is calculated from the test results, which is compared to the maximum allowed acceptance value L1. If the calculated acceptance value is not greater than L1, the test has passed as shown in Figure 3. In this example, the methods for assay and content uniformity are different and the determined correction factor is outside the range of 0.97–1.03. Therefore, the results for the active substance are multiplied by the correction factor in order to calculate the corrected amount.



	A	B	C	D	E
1	**Uniformity of Dosage Units Report**				
2					
3	**General**				
4	**Product Batch Number**	**#123456**	*Target Content T*	102.0	
5	**Peak Name**	**Test Substance**	*Correction Factor*	1.050	
6	*Channel*	UV_VIS_1	*Max. Acceptance Value L1*	15.0	
7	*Dosage Form*	Common Dosage Forms	*Lower Amount Limit*	Not needed if n=10!	
8	*Pharmacopeia*	USP	*Upper Amount Limit*	Not needed if n=10!	
9					
10	**Results**		**n = 10**		
11	*Mean*		105.4		
12	*Standard Deviation s*		2.8		
13	*Reference Value M*		102.0		
14	*Acceptance Value AV*		10.0		
15	**Test Result**		**Test passed**		
16					
17	Replicate ID	Name	Amount	Corrected Amount	Evaluation
18				[%]	
19					
20			UV_VIS_1		
21	1	125µg Tablets Batch #123456	99.0	103.9	n.a.
22	2	125µg Tablets Batch #123456	119.8	105.0	n.a.
23	3	125µg Tablets Batch #123456	100.4	105.4	n.a.
24	4	125µg Tablets Batch #123456	98.5	103.4	n.a.
25	5	125µg Tablets Batch #123456	99.8	110.0	n.a.
26	6	125µg Tablets Batch #123456	103.1	108.3	n.a.
27	7	125µg Tablets Batch #123456	103.4	108.6	n.a.
28	8	125µg Tablets Batch #123456	96.9	101.8	n.a.
29	9	125µg Tablets Batch #123456	97.5	102.4	n.a.
30	10	125µg Tablets Batch #123456	99.9	104.9	n.a.

Figure 3. Content uniformity report for case 1 and n = 10.

The table in Figure 4 shows a failed n = 10 case (acceptance value = 21.7). The test result displays the message “Test additional 20 units!” indicating the requirement to continue the content uniformity test with Stage 2. After the additional units have been analyzed and the results are available, the acceptance value is calculated again. It must not be greater than L1. Additionally, no individual unit may lie outside the interval between lower and upper amount limit. These limits depend on the Target Content and the Mean Value and are calculated automatically. Each result is evaluated as “Pass” or “Fail” (Figure 4).



Uniformity of Dosage Units Report

General			
Product Batch Number	#123456	*Target Content T*	102.0
Peak Name	**Test Substance**	*Correction Factor*	1.060
Channel	UV_VIS_1	*Max. Acceptance Value L1*	15.0
Dosage Form	Common Dosage Forms	*Lower Amount Limit*	77.0
Pharmacopeia	USP	*Upper Amount Limit*	127.0
Results		**n = 10**	**n = 30**
Mean		106.9	106.1
Standard Deviation s		7.0	4.7
Reference Value M		102.0	102.0
Acceptance Value AV		21.7	13.6
Test Result		**Test 20 additional units!**	**Test passed!**

Replicate ID	Name	Amount	Corrected Amount [%]	Evaluation
		UV_VIS_1		
1	125µg Tablets Batch #123456	99.0	103.9	Pass
2	125µg Tablets Batch #123456	119.8	125.8	Pass
3	125µg Tablets Batch #123456	100.4	105.4	Pass
4	125µg Tablets Batch #123456	98.5	103.4	Pass
5	125µg Tablets Batch #123456	99.8	104.8	Pass
6	125µg Tablets Batch #123456	103.1	108.3	Pass
7	125µg Tablets Batch #123456	103.4	108.6	Pass
8	125µg Tablets Batch #123456	96.9	101.8	Pass
9	125µg Tablets Batch #123456	97.5	102.4	Pass
10	125µg Tablets Batch #123456	99.9	104.9	Pass
11	125µg Tablets Batch #123456	99.8	104.7	Pass
12	125µg Tablets Batch #123456	103.6	108.8	Pass
13	125µg Tablets Batch #123456	98.7	103.6	Pass
14	125µg Tablets Batch #123456	100.6	105.6	Pass
15	125µg Tablets Batch #123456	101.3	106.4	Pass

Figure 4. Content uniformity report for case 1 and n = 30.

Figure 5 shows the graphical representation of the results. The lower and upper amount limits are indicated as horizontal lines in the graph.

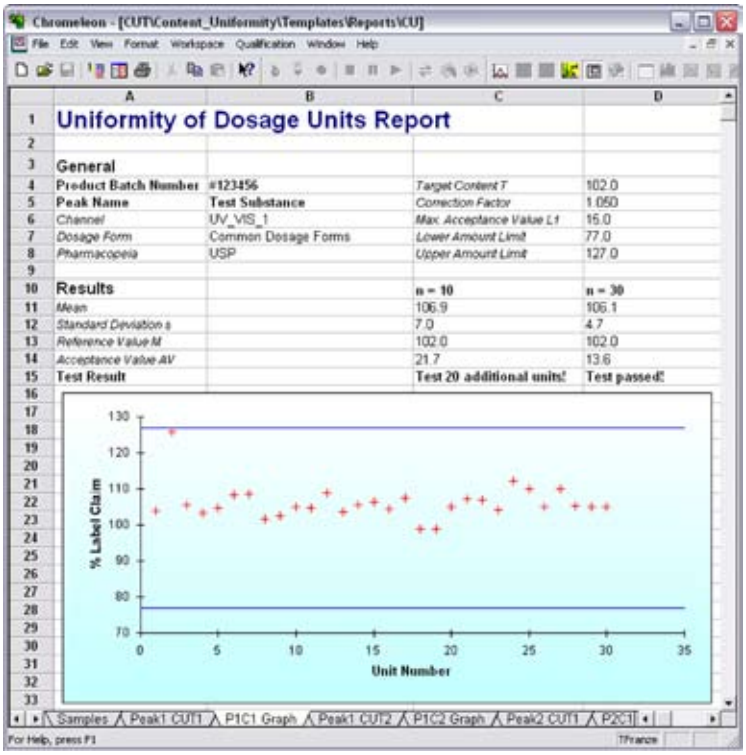


Figure 5. Individual results of content uniformity plot and final test results.

Case 2: USP and Suppositories, Transdermal Systems, and Inhalations Packaged in Premetered Dosage Units

For Suppositories, Transdermal Systems (TDS), and Inhalations Packaged in Premetered Dosage Units, the United States Pharmacopeia has defined individual, although similar, criteria. The criteria for suppositories are stricter than for TDS and Inhalations.

No acceptance values are calculated here. To pass the test, each single result must lie within a certain interval and the RSD must not exceed 6.0 (for n = 10) and 7.8% (for n = 30), respectively. Figure 6 shows how the results of a suppository test are presented in the Chromeleon report. Because one unit was outside the Stage 1 test limits (strict limits, dashed purple lines) and the RSD was above 6.0%, the Stage 2 test had to be performed. All results were within the Stage 2 test limits (wide limits, solid blue lines) and the RSD was well below the Stage 2 limit of 7.8%.

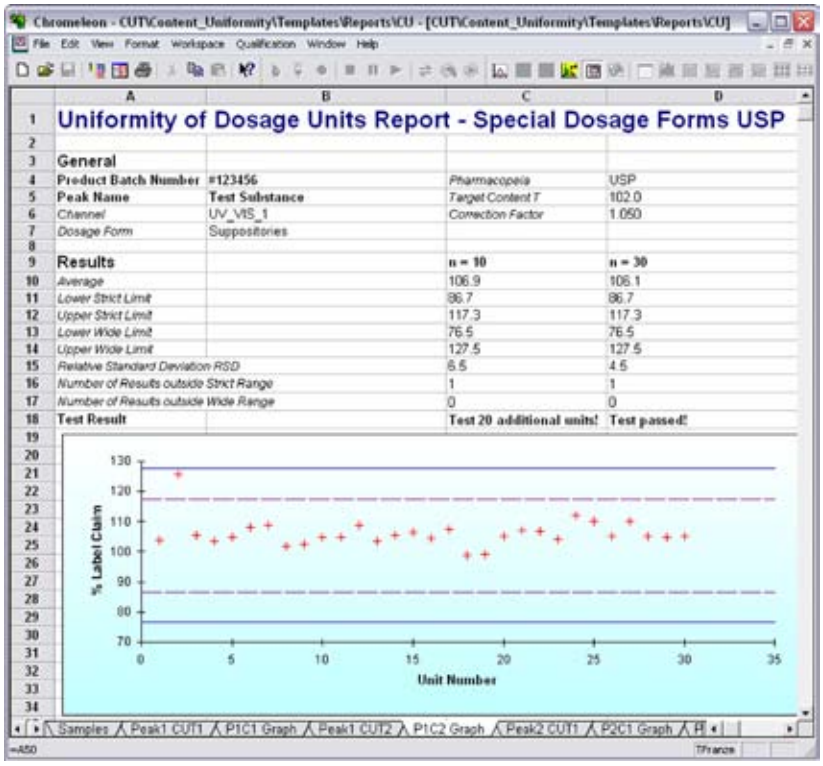


Figure 6. Final test results and plot for Special Dosage Forms.

REPORTING THE SECOND STAGE

If the test of 10 units fails, another 20 units must be tested. For evaluation, the results from the previous test also must be included. Most often these test results are distributed across different sequences.

In order to bring all the data together it is necessary to run a Chromeleon query. For content uniformity testing, the query required is simple and can be easily created using the Query Wizard available in Chromeleon. The necessary information for the query to locate all samples for the content uniformity experiment is the content uniformity test number (CUT_No, in this example 001) and the test stage information (Figure 7). Once a query is run, a virtual sequence (Figure 8) containing all the relevant data is created.

Figure 7. Required steps of the Query wizard in order to collate the required sample data.

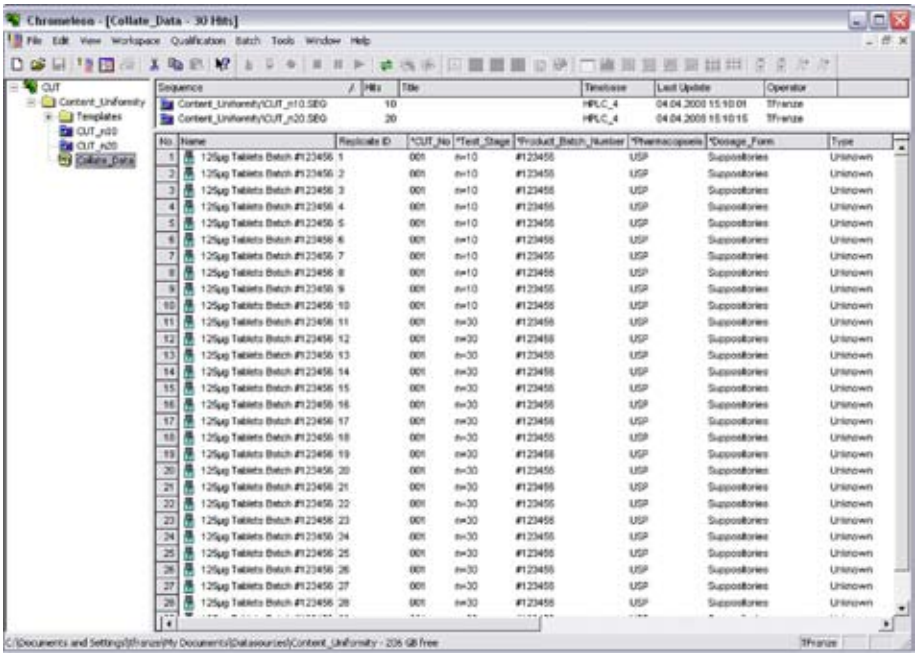


Figure 8. Query result.

This data can then be reported in order to create the final content uniformity report. Chromeleon also supports the creation of an electronic version of the report using the Adobe portable document file format (.pdf). This makes it very easy to distribute the report for review or for inclusion into a data submission package.

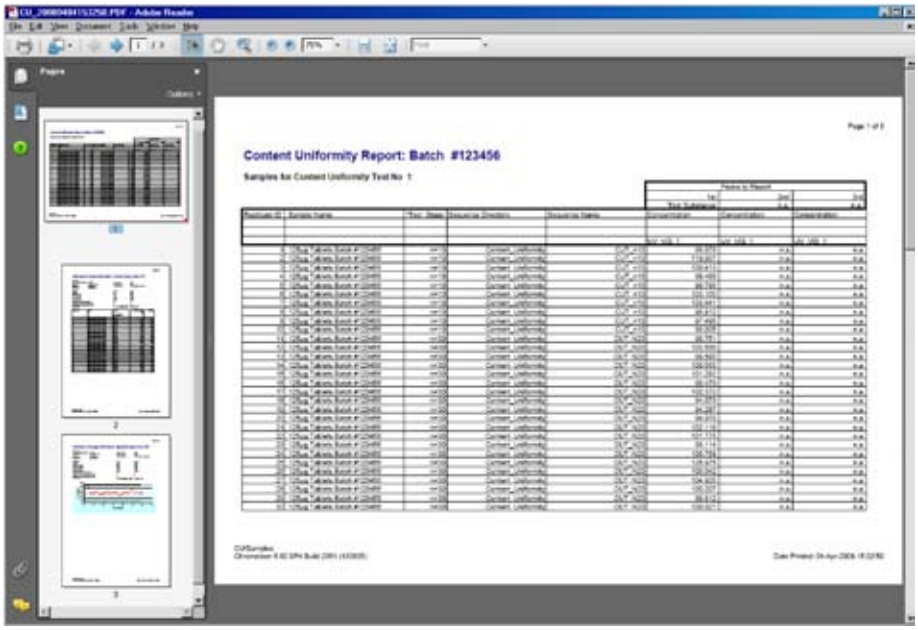


Figure 9. Electronic content uniformity report.

CONCLUSION

The Chromeleon Chromatography Management Software offers a fast and simple way of producing content uniformity reports in accordance with the EP and USP rules. This provides the following benefits to laboratories:

- Increased laboratory productivity—users can spend more time running experiments and less time performing manual data transcription and calculations.
- Increased reliability of results—transcription errors and errors caused by manual calculations are eliminated.
- Faster creation of content uniformity reports—the built-in Chromeleon query function and flexible reporting tool enables content uniformity reports to be created through two mouse clicks.
- Improved distribution of content uniformity reports—the easy creation of electronic content uniformity reports using Chromeleon means that reports can be easily distributed for review.

REFERENCES

1. United States Pharmacopeia USP30-NF25, Chapter 905, Uniformity of Dosage Units, 2008.
2. European Pharmacopeia 6.1, Chapter 2.9.40 Uniformity of Dosage Units, 2008.

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