International Centre for Diffraction Data round robin on quantitative Rietveld phase analysis of pharmaceuticals

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The ICDD sponsored a round robin on the quantitative Rietveld phase analysis of pharmaceuticals. 11 participating laboratories from the pharmaceutical community submitted both raw data and processed quantitative results. The purpose of the round robin was to evaluate current practices in laboratories, so procedures and methods were not specified, but they were recorded. Cluster analysis tools were applied to all the data sets and their use helped identify the root causes of several types of errors in specimen preparation, data treatment, and Rietveld analysis. The authors considered this round robin to be difficult. Sample homogeneity was an issue and molecular orientation was observed in many data sets. Each material studied has structural polymorphs so the selection of starting parameters and their refinement was nontrivial. Similar to prior round robins on inorganic materials and minerals, this round robin identified operator errors as the major contributor to poor results. Four laboratories achieved excellent results on all phases in all three samples, with accuracy within relative errors of 5% to 10%. © *2010 International Centre for Diffraction Data.*
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Key words: pharmaceuticals, quantitative phase analysis, Rietveld analysis, phase identification

I. INTRODUCTION

The quantitative phase analysis by Rietveld method (Rietveld, 1990) has quickly arisen as a favored method for quantitative phase identification by X-ray diffraction (XRD) because of its ease of use. The application of the method itself requires substantial user expertise to obtain accurate results (Madsen *et al.*, 2001; Scarlett *et al.*, 2002). However, the technique has been automated and is widely available in global diffraction analysis software packages, both commercial and freeware. With highly automated commercial software, results can often be achieved within minutes of data collection. Typically the most time consuming step in a Rietveld analysis is the author's interpretation and satisfaction with the results. A prominent feature of the Rietveld method is that a quantitative result can be achieved from a single experimental diffraction pattern and often differentiates this method from standard addition and pattern fitting quantitative analysis methods which may require multiple data sets and/or experiments.

The accuracy and precision of the Rietveld method have been extensively studied for inorganic materials including international round robins (Madsen *et al.*, 2001; Scarlett *et al.*, 2002), minerals (Gonzalez *et al.*, 2003; O'Connor and Li, 2000; O'Connor and Li, 1998; Winburn, 2003) and coal, and its combustion products (Gonzalez *et al.*, 2002, 2003). Pharmaceuticals analyses are typically more problematic as many of the factors that are known to contribute errors in inorganic Rietveld quantitative analyses (Winburn, 2003; Webster *et al.*, 2003) are commonplace occurrences in pharmaceutical analyses. These factors include the presence of asymmetric crystals that are highly oriented, the presence of amorphous or nanocrystalline phases, and the increased occurrence of disordered materials and polymorphs. In addition, pharmaceutical analyses present more challenges in terms of known instrumental errors. The diffracting power and mass attenuation coefficients of organic materials often lead to substantial specimen displacement and zero point errors that need to be accounted for. Because of these errors many pharmaceutical specimen preparation methods are based on thin film or capillary techniques where small amounts of specimen are analyzed, so the analyst has to be concerned about the influences of particle statistics and the representative sampling methods used to obtain the specimen from the bulk material.

Because of the additional considerations in the quantitative phase analysis of pharmaceutical materials the International Centre for Diffraction Data (ICDD) conducted a round robin starting in 2006 of interested international participants in conjunction with the Pharmaceutical Powder X-ray Diffraction (PPXRD) symposia series. Multiple data sets were collected on three different samples from 11 participating laboratories and the results are presented here.

II. EXPERIMENTAL

The objectives and methodology used for this round robin were discussed and debated by the attendees of PPXRD-6 and PPXRD-7 held in Barcelona, Spain and Orlando, Florida, respectively. ICDD staff scientists facilitated the discussions (Faber and Needham, 2008; Faber, 2007). Prior to PPXRD-7 samples were prepared for the round robin for distribution at the conference. The ICDD also contacted interested attendees from PPXRD-6 and encouraged their participation. Results and conclusions were presented at PPXRD-8 (Needham *et al.*, 2009) held in Glasgow, Scotland.

The attendee discussion revealed that Rietveld practitioners in the pharmaceutical industry were using a wide variety of instrumentation, specimen preparation methods, and software analysis packages to perform quantitative phase analysis. A primary objective of the round robin was to allow each

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TABLE I. Selected variables for each participant in the round robin. Cavity refers to a cavity mount where specimens are usually mounted in a deep cavity.

Id	Specimen	System	Goniometer	Wavelength	Spin	Software
0	Cavity	BrukerD8	θ-θ		Yes	GSAS
2	Cavity	BrukerD8	θ-θ	Cu $Ka1$/Cu $Ka2$	Yes	FULLPROF
3	Capillary	TTRAXIII (Rigaku)	θ-θ	Cu $Ka1$/Cu $Ka2$	No	GSAS
4	Zero background	ARL X'tra XRD	θ-θ	Cu $Ka1$/Cu $Ka2$	Yes	JADE 8.5
5	Cavity-side filled	Rigaku D-Max III B	Vertical	Cu $Ka1$/Cu $Ka2$	No	RIGAS 5.0
9	0.4 mm OD, 0.01 MM wall thickness glass capillary	PANalytical X'Pert Pro MPD	θ-θ	Cu $Ka1$/Cu $Ka2$	Yes	PANALYTICAL HIGH SCORE PLUS V2.2.0
11	The powder is filled between two Mylar foils with a 8 mm diameter mask	STOE STADIP transmission diffractometer		Cu-$Ka1$	Yes	RIETVELD PROGRAM SIROQUANT® VERSION 3.0
12		PANalytical		Cu $Ka1$/Cu $Ka2$	Yes	RIETVELD
17	Cavity	PANalytical X'pert ProMPD	θ-2θ	Cu $Ka1$/Cu $Ka2$	Yes	RIR
18	Cavity	Rigaku D5005	θ-2θ		No	JADE 8.0
19	Kapton capillary	Synchrotron		0.400 06 Å	Yes	GSAS

laboratory to evaluate the success of their quantitative analysis procedure by evaluating standard materials. Therefore critical variables were not specified as part of the round robin procedure but each participant was asked to record instrumental conditions, specimen preparation methods, and analysis methods used to process the data. A data collection and analysis worksheet was given to all the participants in order to record the selection of instrumental, specimen preparation, and data analysis variables.

Three materials were chosen for the round robin; these were (a) D-mannitol, (b) acetaminophen, and (c) silicon. Three samples were made from these materials which were combinations of (a) and (c), (b) and (c), and a three phase mix of (a), (b), and (c). The silicon selected was NIST Standard Reference Material 640c, so that this material could be used as an internal standard calibrant in each mixture. D-mannitol and acetaminophen were both supplied by Sigma-Aldrich and specified as equal or greater than 99% pure. The materials were carefully weighed on an analytical microbalance and then mixed with a vortex mixer. The mixer homogenized the samples but did not greatly reduce the particle size. From the master batch, aliquots of 1 g each were dispensed in sample bottles and distributed for analysis. Each bottle was numbered and each participant was given a laboratory number so that they could track their results in subsequent presentations and publications.

A total of 16 sample sets were delivered to participants and a total of 11 laboratories returned a set of results. The results consisted of the submission of electronic raw data files, the data collection and analysis worksheet, and the final quantitative analysis results reported in weight percent. A few laboratories submitted multiple data sets for each specimen, as they may have tested several variables in the analysis. In total, 69 data sets were received and analyzed.

The participating scientists and laboratories are as follows:

- Y. Ososkov and Z. Cherbanyk Beti, Exova, Mississauga, Canada
- A. Patel, Bristol-Myer Squibb, New Brunswick, NJ, USA
- J. Wright and A. Fitch, European Synchrotron Radiation Facility (ESRF), Grenoble, France
- P. Varlashkin GlaxoSmithKline, Durham, NC, USA
- F. Needham, ICDD, Newtown Square, PA, USA
- M. Ermrich, Roentgen Laboratory, Reinheim, Germany
- X. Bokhimi, Universidad Nacional Autonoma De Mexico, Coyoacan District, Mexico
- R. Suryanarayanan, University of Minnesota, College of Pharmacy, Minneapolis, MN, USA
- J. Henao, Universidad Industrial de Santander, Columbia
- E. Wachtel, Weizman Institute of Science, Rehovat, Israel
- H. Brusova, Zentiva AS, Prague, Czech Republic

The participants were asked to choose the "best methods" used in their laboratories. Table I presents the recorded selections of specimen preparation, instrument conditions, and analysis software.

The raw data scans were analyzed using two software programs containing cluster analysis algorithms. The analyses were performed at the ICDD using the submitted raw data. Data sets were input into PANALYTICAL HIGH SCORE PLUS VERSION 2.2.B and analyzed in the cluster analysis module. The data sets were also input into BRUKER-AXS POLYSNAP VERSION 2.1.1. The raw data were submitted in a wide variety of format types and both programs could read the majority of the data formats, but neither could read them all. Fortunately the combination of the two cluster analysis programs was able to read all formats of all the submitted data.

III. RESULTS

The raw data and the quantitative phase identification results were analyzed separately. The authors hoped that by separating the analyses and examining the data that they could separate out the influence of different variables used in the round robin. Specifically the authors were trying to isolate specimen preparation and sample errors from instrumental errors and finally from data processing errors. This was done deliberately because prior quantitative phase identification results strongly suggest that operator errors are the largest source of errors in quantitative analysis (Scarlett and Madsen, 2001 and references therein). Throughout this presentation the authors will use definitions recommended by Jenkins (Jenkins and Snyder, 1996) in that a specimen is

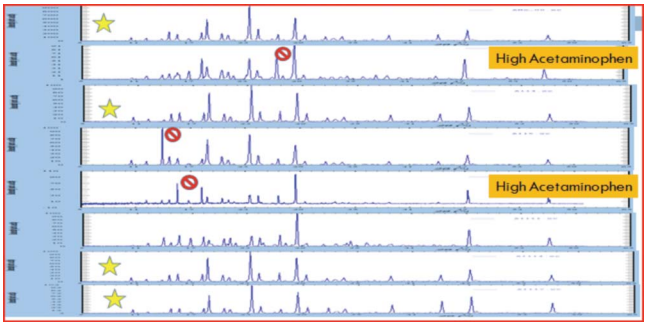

Figure 1. (Color online) Raw data from eight laboratories placed on similar scales for the three component mixture of acetaminophen, mannitol, and silicon.

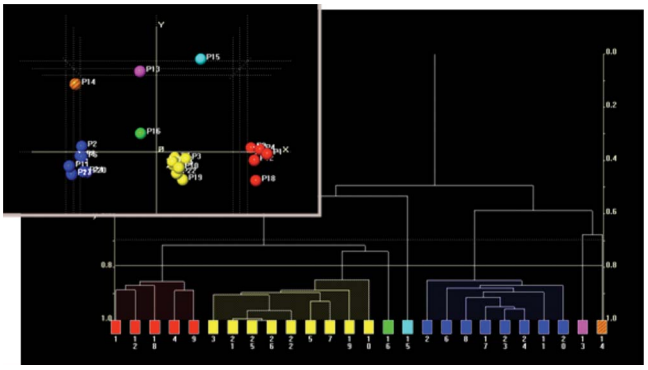

Figure 3. (Color online) Dendrogram and principal component analysis of 21 data sets from seven laboratories.

defined as the material presented in the instrument for analysis and a sample refers to the bulk material used in the round robin.

A. Sampling and orientation

Upon reviewing the initial raw data from all the participants it was immediately apparent that there were some issues with sampling and molecular orientation. As shown in Figure 1, there is evidence of both potential sources of error in the raw data. There are four data sets that have nearly identical scaled diffraction patterns; these are starred and one would anticipate that they would produce similar analytical results. There are three patterns with a stop sign. The second and fifth patterns exhibit stronger reference peaks for the pattern of acetaminophen (see Figure 2). The fourth pattern from the top has a very intense peak to the left of the stop sign indicative of molecular orientation. If one looks at the three patterns with stop signs, one would expect different quantitative results.

Figure 3 shows the dendrogram and principal component analysis (PCA) for 21 data sets. The analyses immediately identify three sets of similar data which are shown to be correlated in both graphic representations. These three sets correspond directly to the three different phase compositions analyzed in the round robin. The yellow colored data sets are the three component mixes (a, b, and c) and it is flanked by the red and blue clusters of the two component mix. The cluster analysis routine immediately isolates four data scans which do not cluster and upon examination of the diffraction patterns one corresponds to a nonrepresentative specimen and the other three to very high resolution data sets from laboratory 9.

Another PCA analysis of 63 data sets from nine laboratories is shown in Figure 4. In this analysis both the dendrogram and the PCA divided the data into a large number of clusters. The clusters corresponded to the original three mixtures but also separated out some specimen groups based on instrumental artifacts. This was determined by cross referencing each cluster point with its designated diffraction pattern. Some of the common groups were labeled by the authors in Figure 4. Synchrotron data with extremely narrow diffraction peak widths cluster as a separate group. Another participant used large incident beam slits producing a very high background with a strong slope towards lower angles. A third participant's data exhibited scattering artifacts, most probably from the beam stop, at low angles.

Both Figures 3 and 4 are output graphics from cluster analysis programs. As defined by the program, the dendrogram shown in Figure 3 uses hierarchal agglomerative clustering to group data sets. All data scans are compared to each

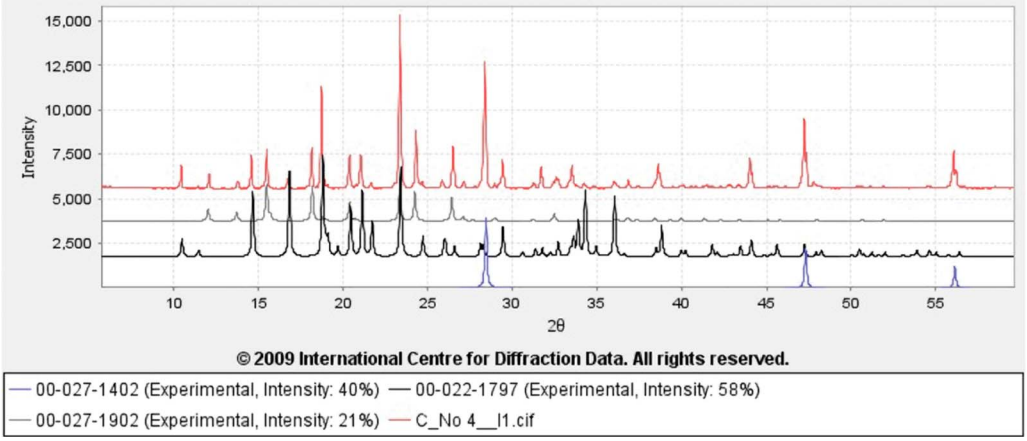

Figure 2. (Color online) Phase identification of the three component mix. The experimental data are shown as the top scan and the three identified phases are shown as digital simulations in the three scans below the top scan. In these data the doublet centered around 18° 2θ (Cu) in the top scan has a contribution from each of the two major pharmaceutical phases shown in the next two scans.

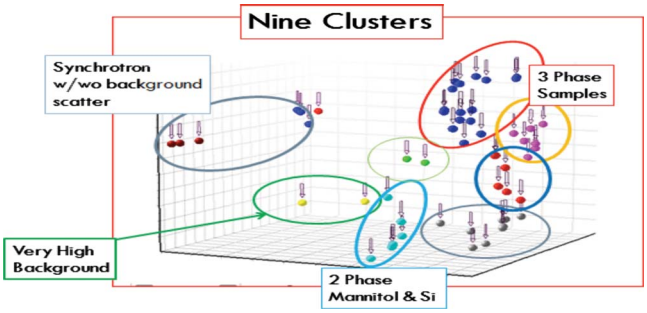

Figure 4. (Color online) PCA of 63 data sets from nine laboratories. The comments were added by the authors.

other in a correlation matrix representing a similarity between any given pair of scans. The output of the hierarchal agglomerative clustering put the scans in different classes defined by similarities. Figure 4 is a PCA plot which also uses output from the correlation matrix. The output from the correlation matrix is expressed in a series of eigenvalues which are based on systematic variances in large sets of observations. The PCA is a representation of the first three eigenvalues calculated for each data set.

In Figure 3 the cluster analysis software removed the background data and renormalized the data sets. In Figure 4 the background data were not removed and the cluster analysis routines were more sensitive to instrumental variations. Both programs had the ability to remove background effects so the results are more a function of the authors' selections than the capability of the program. However, running the data sets with and without background correction also shows the importance of background selection and removal for quantitative analysis.

The data presented in Figure 5 are all evidence of poor crystallite distribution and large crystallites present in the specimens analyzed by the participants. The data on the extreme right are not representative of the round robin but do represent the worse case that could occur is the specimen was not prepared properly. It was recommended that the participants grind the specimens prior to the analysis but they were cautioned not to grind heavily since the silicon added to

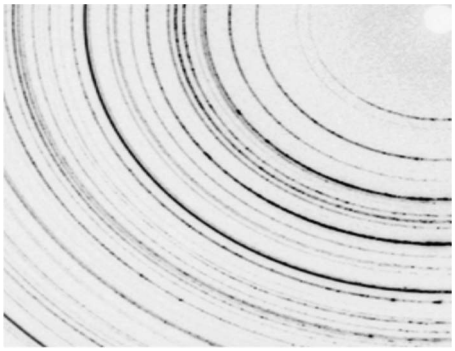

Figure 6. Two dimensional pattern for the mixture of silicon and mannitol. While not as severe as the effects shown in Figure 5 for acetaminophen, the mannitol exhibits grainy behavior as well.

the specimen can act as a grinding aid to grind the softer pharmaceutical materials. This created a dilemma for the participants in balancing the observed orientation and grain statistics issues and not destroying the crystallinity of the materials being studied. Unfortunately these effects were discovered after the round robin analysis (Figure 6). In retrospect it would have been preferable to grind the pharmaceuticals first and then coblend the silicon prior to vortexing.

B. Data treatment

NIST SRM 640c was deliberately added to each sample so that the participants could calibrate their experiments and correct the data for common instrumental and specimen errors. In Figure 7 several participants' data were overlaid showing the silicon 220 reflection. The broad range of 2θ values with both positive and negatives deviations from the certified position are classic examples of specimen displacement errors. Some of the positions deviate as much as 0.20°, which would impede Rietveld refinement and/or phase identification if not corrected. The data scan in dark blue on the far left indicates a severe zero point shift. This was a data set from a capillary mount indicating that the specimen was not

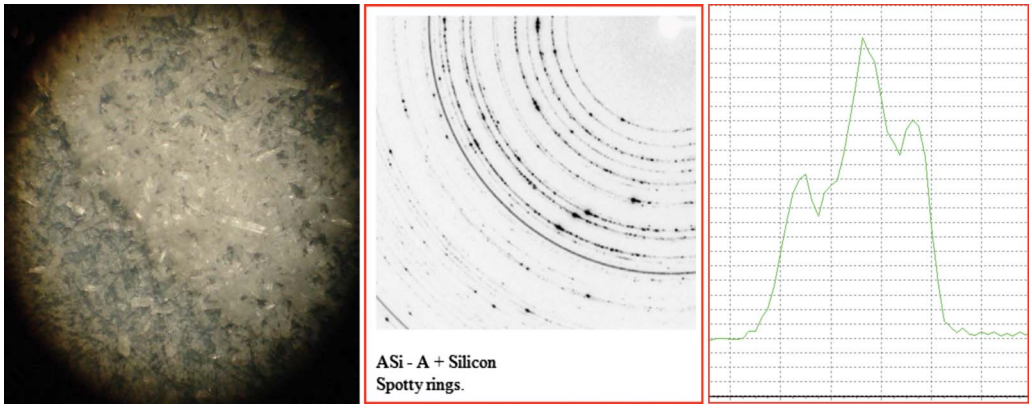

Figure 5. (Color online) Specimen orientation; on the left a light microscopy photograph of the acetaminophen used in the round robin; large asymmetric platelets are clearly visible. In the middle is a 2D XRD pattern of the mixture of acetaminophen and silicon. The silicon pattern shows well dispersed crystallites in the uniform Debye ring near the center of the pattern. Acetaminophen Debye rings are highly spotted and occasionally intense indicative of poor distribution and large crystallites. The data on the right are from a participant's data submission where one of the major diffraction peaks of acetaminophen is exhibiting nonrandom diffraction.

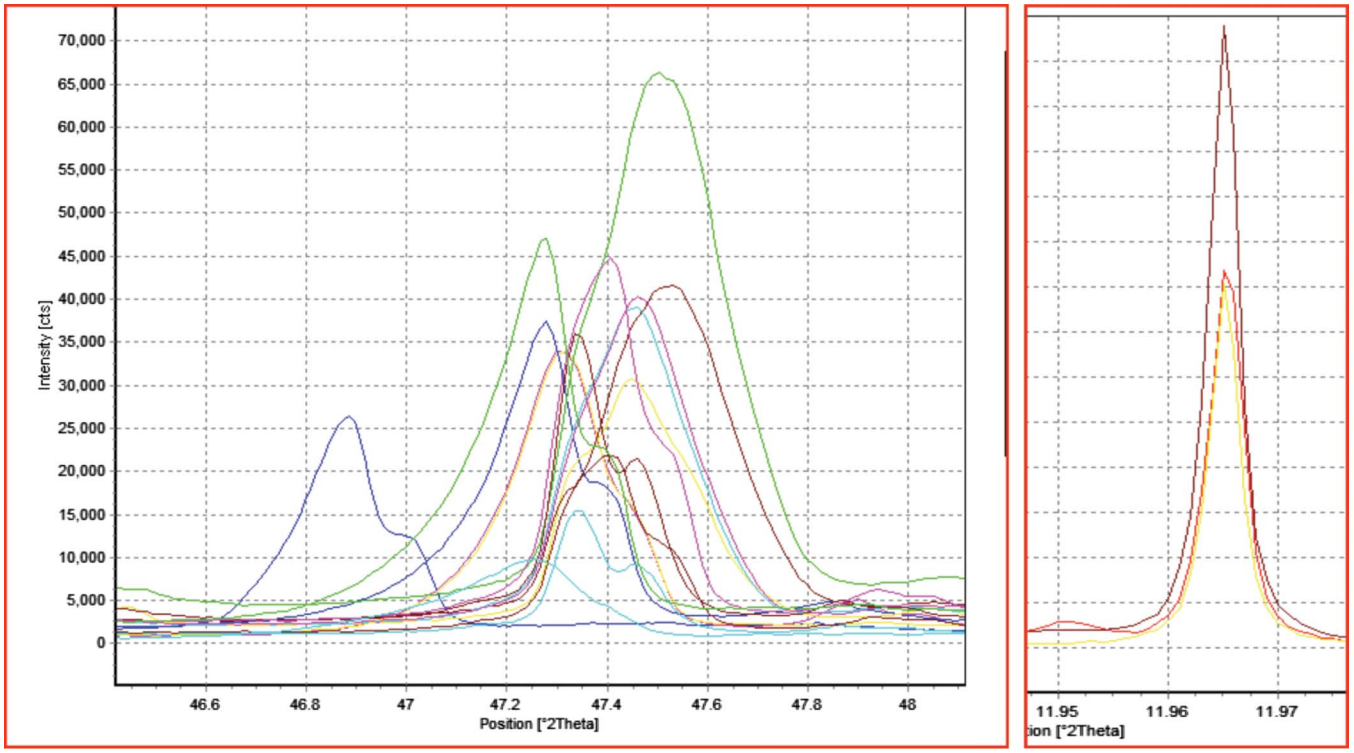

Figure 7. (Color online) Multiple data scans from round robin participants showing the 220 reflection of silicon; displacement errors are evident from the wide range of positions. NIST SRM 640c was the source of silicon. For comparison the same reflection is shown using monochromatic radiation taken at the ESRF where one can see the significant improvement in resolution.

located at the true focusing center of the goniometer. It was not recorded whether the participants calibrated their data using the silicon SRM. If they did not, one can see that this would have been a significant source of error.

As previously mentioned several data sets exhibited nonlinear backgrounds, as the participant used different slit settings in their experiments. Other data sets exhibited scattering artifacts. These would also be sources of error if not accounted for (removed) in the Rietveld refinement.

C. Phase identification

Papers on Rietveld refinement rarely discuss the importance of phase identification; it is frequently assumed that the user knows the material and is able to choose the right crystal structure to use for the starting parameters of the Rietveld refinement. In this round robin, three materials were selected that have a range of polymorphs as well as a range of possible crystal structure candidates.

In Rietveld refinement programs a scale factor is calculated from the input crystal structure. Prior to the refinement this should be conceptually similar to the I/Ic value, another scaling factor, that is calculated from the crystal structure. For the materials used in this round robin the range of published I/Ic values is shown in Table II. The wide range is due to the fact that these commercial materials have been widely studied, multiple polymorphs have been identified, and the materials have also been studied as a function of temperature and pressure. For pharmaceutical materials, many single crystal analyses are performed at low temperature to freeze molecular motions and get more accurate determinations. However this also shrinks the unit cell and increases the scale factor. Care has to be taken to select the correct polymorph for ambient temperature determinations. If one selects the ambient temperature stable form of cubic silicon, the candidate list would reduce to 18 candidates selections and *everyone* has an I/Ic of 4.55. If the proper polymorph and temperature are selected for acetaminophen then the I/Ic is 0.62. The phase identification process takes the guesswork out of the selection. As shown in Figure 2, the results of a search/match identification on the test samples will direct the user to the best "fits" among the candidate choices, which are the correct ambient temperature polymorphs. To verify this assumption four different data sets from participating laboratories were run through search/match programs at the ICDD.

TABLE II. Polymorphs of mannitol, acetaminophen, and silicon.

Material	Material used	Polymorphs	Candidates[a]	Range I/Ic
Mannitol	Beta-D-mannitol	Alpha, beta, gamma	12 references	0.48–0.66
Acetaminophen	Monoclinic, form I	Form I, II	15 references	0.50–1.03
Silicon	Cubic, SRM 640c	Cubic (2), hex, tetragonal	29 references	1.98–4.55

[a]Reference PDF entries found in Release 2008 PDF-4+ or PDF-4/Organics.

TABLE III. Submitted results on three round samples from 11 participating laboratories. The control is the weight percent of each material that was added to each sample.

	Sample 1		Sample 2		Sample 3		
Laboratory	Mannitol	Silicon	Acetaminophen	Silicon	Mannitol	Acetaminophen	Silicon
Control	85	15	85	15	40	45	15
18	66	34	33	66	48	8	44
2	44	56	46	54	23	29	49
9	87	13	75	25	23	66	11
4	83	17	78	22	51	33	16
12	92	8	82	18	63	28	9
11	85	15	83	17	42	42	16
0	87	13	87	13	39	49	12
19	86	14	87	13	40	46	14
3	82	17	87	13	44	43	13
17	95	5	90	10	55	40	6
5	75	25	92	8	43	50	7

Identical solutions were identified. In PDF-4+ the users can directly access the atomic coordinates and in PDF-4/Organics cross-references are given for the appropriate reference in the Cambridge Structural Database. One outcome of this round robin was that the ICDD realized that it did not have all the NIST SRM inorganic materials represented in PDF-4/Organics. This oversight will be corrected in PDF-4/Organics Release 2010 when the calibration standards were added to this product.

The incorrect choice of polymorph or a temperature modified structure may result in significant errors. This is particularly noticeable for silicon since the overall scale factor for silicon is approximately 7.3× that of acetaminophen. A small error in the determination of silicon can lead to a large error in the quantitative results. If a nonambient temperature structure is selected for the starting parameters in the Rietveld refinement then errors in the analysis *will occur* unless the user adjusts the unit cell, temperature factor, and scale factors in the refinement.

IV. DISCUSSION

Table III shows the round robin results. The data in the table were specifically sorted by the weight percent silicon determined in sample 2. This sorting was selected due to the clear evidence of specimen orientation observed in many data sets and the accompanying microscopy and 2D diffraction data shown in Figure 5 indicating both poorly distributed grains and large grains due to the asymmetric nature of the crystals.

When sorting the data in this manner the round robin participants divide into different subgroups. Four laboratories achieved excellent results (laboratories 11, 0, 19, and 3). These four results are highlighted in the table. You can see from the table that for these four laboratories the seven quantitative measurements in the three samples were within 4% absolute of the control and 5% to 10% on a relative basis. As demonstrated by sample 2, all these laboratories would have successfully corrected their data for the observed orientation effects. Three of these four laboratories used the program GSAS which contains two types of orientation corrections. GSAS is also famous (infamous) for its lack of automation and large array of variables that the user can select in performing an analysis. The round robin demonstrated the power of this program in the hands of knowledgeable users. These four laboratories also used four different specimen preparation methods (cavity, thin film, glass capillary, and Kapton capillary). The authors assume that since these laboratories got accurate results they were able to overcome the known problems with these preparations, which are specimen displacement errors in cavity mounts and particle sampling and statistics in thin film and capillary mounts. The former can be adjusted by using the silicon calibrant, while the latter can be improved by specimen grinding prior to the analysis and spinning during the analysis. All four of these laboratories reported using a specimen spinner in the sample stage.

A second group of laboratories, numbers 18 and 2, consistently overestimated the amount of silicon in each of the three samples. As mentioned in Sec. III, since silicon is a strong coherent scatterer, scale factors are large and small errors can be magnified. The selection of the appropriate structure is critical and key parameters such as scale factor, temperature factor, and unit cell dimension may be of required refinement. These participants used a cavity mount and the data would need to be corrected for displacement shifts and other known instrumental errors using the silicon as an internal standard. The cluster analyses clearly showed that the three component mixture (sample 3) of laboratory 18 was a nonrepresentative specimen from the distributed bulk sample (i.e., did not cluster); the raw data from the specimen would not be expected to produce a result representative of the bulk sample.

The data from laboratory 4 exhibited severe orientation, especially in sample 1, and laboratories 5 and 9 showed a severe orientation in the raw data in sample 3. For laboratory 4 the oriented phase was mannitol and these laboratories achieved a reasonable result considering the severity of the orientation. This case shows the benefit of Rietveld refinements in using the whole pattern for the refinement. The data from laboratory 4 on sample 3 indicated a nonrepresentative specimen. The results reflect the raw data but not the bulk sample. The data from laboratory 9 on sample 3 were very

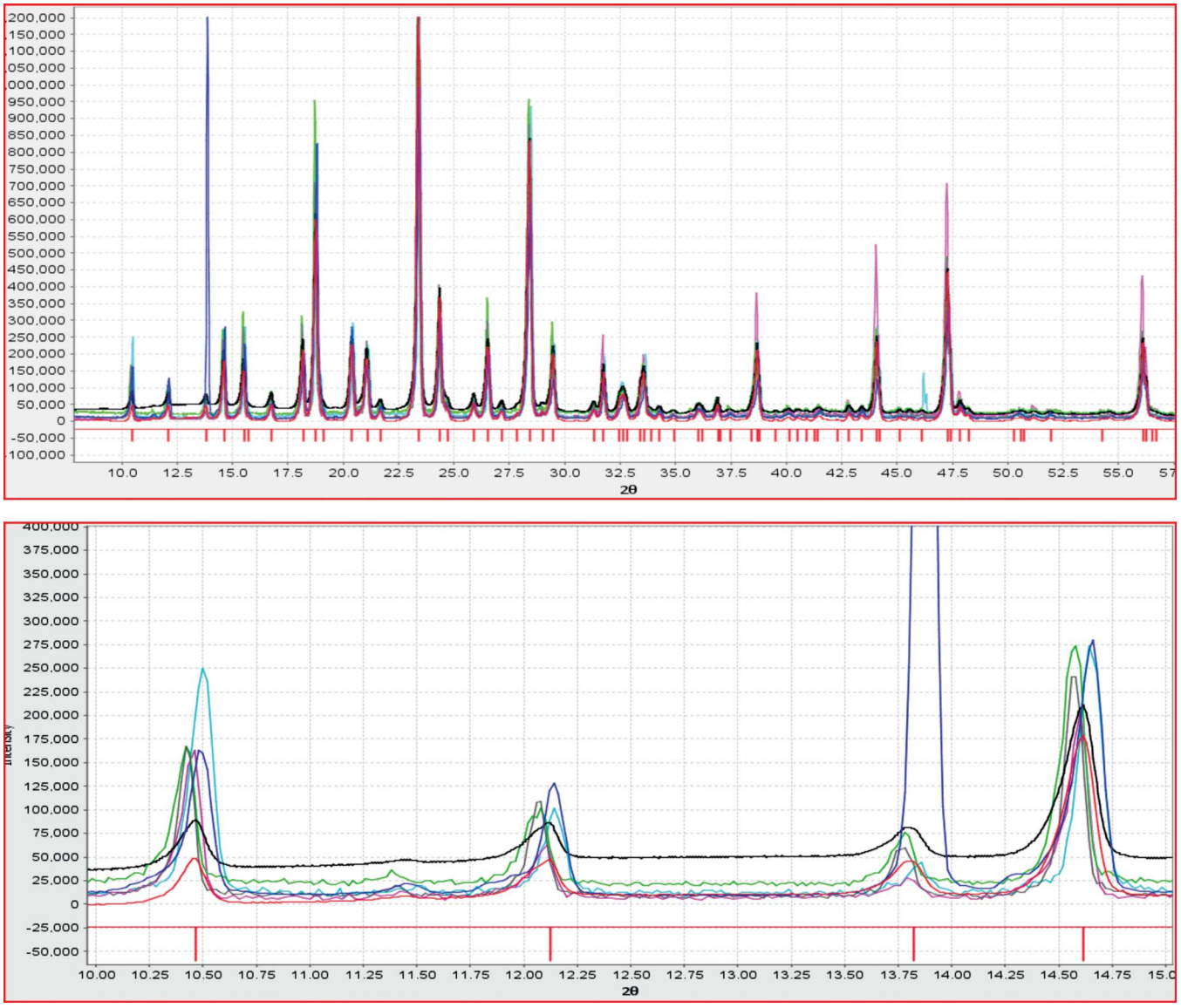

Figure 8. (Color online) (a) Superimposed data from seven laboratories for the three component mixture that were all scaled to the maximum peak. (b) Data from seven laboratories are superimposed for the three component mix. The outside two peaks are due to mannitol and the inside two peaks to acetaminophen. The off-scale peak is characteristic of severely oriented acetaminophen.

high resolution data taken on a small diameter capillary; however, the intensity scale was relatively low and the analysis may have been compromised by the small specimen size resulting in a nonrepresentative specimen in the capillary and orientation.

Laboratory 17 was a special case in that this laboratory used the reference intensity ratio (RIR) method of analysis (Hubbard *et al.*, 1976). The programs used calculated an integrated intensity as a percentage of the pattern and then the I/Ic values calculated from single crystal references were used for the quantitative determination. This is a modified RIR method in that a total pattern versus selected peaks is used to get the pattern intensity. Since a total pattern is used the influence of orientation is somewhat modified but is not analytically measured. However careful examination of the raw data indicates that the mannitol pattern in the three component mixture exhibits a severe orientation resulting in the overestimation of the mannitol phase. Using the same methodology on raw data on the three component mix from laboratory 0 resulted in quantitative results of 42%, 52%, and 6% for acetaminophen, mannitol, and silicon, respectively.

Of the three samples, the mannitol and silicon mixture (sample 1) exhibited the fewest orientation and sampling problems. Most of the submitted raw data, with the few exceptions noted above, are nearly superimposable. Therefore much of the variations observed in the summary of results in Table III are an artifact of how the data are processed.

Sample 3 had the worst sampling and orientation problems. The fact that two of the three components were of needle/platelet morphology challenged the participants in their preparations of a representative specimen. The results reflect the difficulties in producing a homogeneous random specimen. The nonhomogeneous nature of the specimens reflects in the raw data shown in Figures 8(a) and 8(b) and this obviously affected the final results. Laboratories 9 and 5 both showed strong acetaminophen orientated phases in the raw data and this was reflected in higher concentrations in the final results.

V. CONCLUSIONS

The round robin was a tremendous learning experience. The samples were challenging and the analyses and their interpretations were nontrivial. Despite challenges in all the steps of the analyses including specimen preparation, data treatment, and Rietveld refinement, excellent results were achieved by four out of 11 laboratories.

The purpose of the round robin was not to define best practices, but to evaluate the state of analysis and evaluate procedures used in pharmaceutical laboratories. Laboratories were asked to use their standard procedures and record the results. The diversity in the quantitative analysis results from the round robin reflects the diversity observed in specimen preparation and analysis methods. The fact that a group of four independent laboratories achieved excellent results suggests that the technique is robust and standardized practices would be expected to yield reproducible accuracy and precision.

Cluster analyses proved to be a valuable tool for analyzing the data. Sampling inhomogeneities, variable instrument settings, and data artifacts were quickly identified as outliers. The detailed analysis of data groups within and without clusters enhanced the ability of the authors to identify the root cause of several errors and isolate which errors are attributable to preparation, data treatment, and analysis. Many classic errors were identified such as specimen displacement and zero point shifts, particle inhomogeneity, poor counting statistics, molecular orientation, and the improper selection of the starting atomic structure and parameters.

Similar to prior Rietveld round robins on quantitative analysis (see references) the operator error was identified as the largest contributor to poor results. This should not be a surprise considering the huge amount of variables under the operators control in going from specimen preparation to data treatment and then the proper selection of Rietveld refinement parameters. The ICDD teaches or sponsors Rietveld analyses in annual workshops and clinics and it usually takes several days of intense instruction to provide a user basic familiarity with the theory and applications.

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