Holy #$%@!
What Have We Gotten Ourselves Into?

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Bioanalytical “Rules” in 2011

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Holy #$%@!
There are a lot of RULES!

How did we ever get so many RULES?

It wasn’t supposed to be this way!

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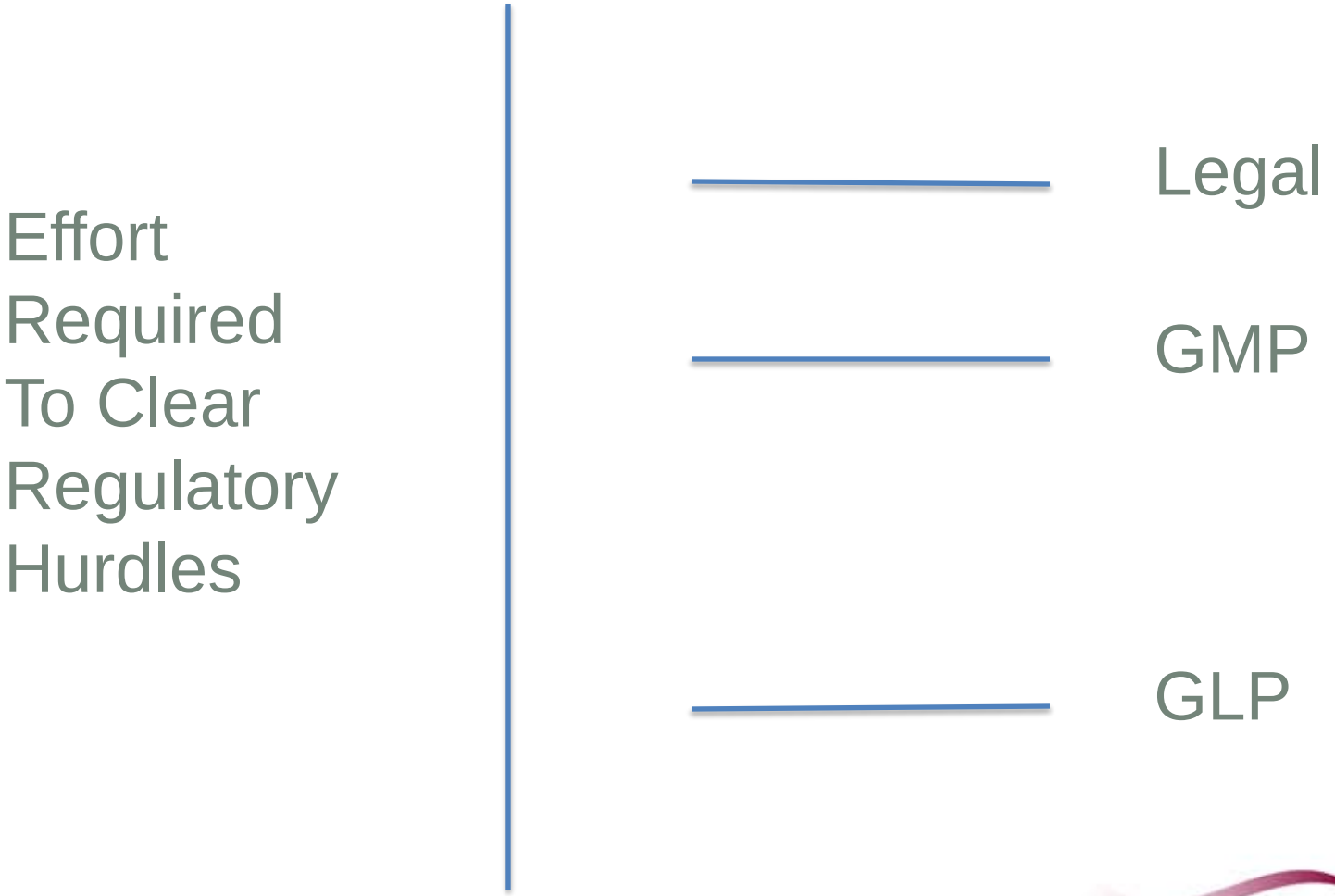
The Perceived Regulatory Hurdles in 1990



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December 1990
1st Crystal City Meeting

- Only attendees were from Big Pharma & FDA – not a lot of us left anymore!
- Meeting severed as the cornerstone for subsequent bioanalytical guidelines and rules
- What were some of the basic philosophies about bioanalysis during that meeting?
  - We did not want to be GMP-like: too many calibrations, too many system validations, too many rules!
  - The GMP analytical process that used a single standard required all of these rules
  - GMP analysis is more critical than bioanalysis because if the GMP analysis is wrong people could be mis-dosed
  - We wanted to create a process that was **self-validating** on a daily basis

1st Crystal City Meeting
Bioanalytical Landscape

- Bioanalytical work was dominated by HPLC-UV:
  - Best LLOQ was about 1 ng/ml
  - A batch/analytical run usually wouldn't exceed 96 samples.
- Almost all bioanalytical work was performed by pharmacokineticists – ±15% is good enough
- The concept of computer validation did not exist
- GLP perception then = documentation
- GLP today:
  - Say what you're going to do (plan/protocol)
  - Do what you said you're going to do
  - Document it!

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1st Crystal City Meeting
Bioanalytical PHILOSOPHY

- Didn't want to be like GMP where we have to calibrate everything
  - Besides it you calibrate in January and everything is OK and then you calibrate in July and it is out of calibration – when did it go out of calibration?
- **Bioanalytical Batch/Run was created so that it would be a real-time self-validating process**:
  - For example, if your pipette volume was fluctuating, if your HPLC pump pressure wasn't steady, if your integrator wasn't integrating consistently, etc, then:
  - Your standards and QCs wouldn't pass acceptance criteria and you wouldn't get smooth PK profiles

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So if a bioanalytical batch/run is a real-time self validating process then why do we have so many rules?

1 Reason = Generic Drug Industry

Why do we have so many bioanalytical rules?

- #1 REASON = GENERIC DRUG INDUSTRY
  - For NDA work, PK analysis is a powerful tool but bioanalysis isn't as important as safety & efficacy data
  - For an ANDA you need two things: a GMP formulation and bioequivalence! Suddenly PK and bioanalytical are almost as important as GMP
  - Bioanalytical/PKists did some stupid things:
    - If you just missed passing BE criteria on Cmax then with a ±15% assay variability, if you carefully selected Cmax samples for repeat analysis you just might get your BE study to pass
    - Ah-ha the BE study failed on Cmax because you diluted your Cmax samples. So extend the ULOQ so you don't have to dilute Cmax samples. Led to problems with carry-over, not enough QCs near the concentration of most of your study samples
    - Etc.

Why do we have so many bioanalytical rules?

- #1 REASON = GENERIC DRUG INDUSTRY
- #2 = Some bioanalysts cheated:
  - Low QCs fail – let's redraw baselines so they pass
  - Don't like PK values – let's redraw baselines
  - If QCs did not pass acceptance criteria in the original injection then lets re-inject the QCs at the end of the batch (next day) to "push the batch to pass"
  - Screen multiple lots of matrix and use only those that are acceptable for validation
  - Etc.

Why do we have so many bioanalytical rules?

- #1 REASON = GENERIC DRUG INDUSTRY
- #2 = Some bioanalysts cheated:
- #3 = Unsophistication of some auditors (external and internal QA) who requested that CROs perform a process that was not good science. Failure of CROs to reject such requests
  - Reanalyze Cmax samples until BE study passes
  - Don’t dilute Cmax samples
  - Etc.

Purpose of this Presentation

- I don't want to just stand up here and complain!
- I think that the bioanalytical community should come together and reject "rules" that do not make scientific sense or require tremendous effort for minimal value
- It's been done before!
  - GMP analysis rules in 2005 suggested that release testing for early development formulations should be similar to commercial release testing
  - GMP community stood up and said "BS" – rules were changed to "phase appropriate testing"

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Bioanalytical rules that do not make sense!

- Performing stability tests in the presence of co-administered drugs.
- Selectivity testing of co-administered drugs when using LC-MS/MS
- If Long Term Stability (LTS) has been established in one lab then why do you have to prove LTS in another lab?
- Manual reintegration “is cheating”
- K^2-EDTA is different than K^3-EDTA and Na^+-Heparin is different than Li^+-Heparin
- Thou shall not reanalyze samples in a BE study for PK reasons
- Freezer mapping
- Event Resolution – MUST identify the root cause!
- Emphasis on recovery
- Etc.

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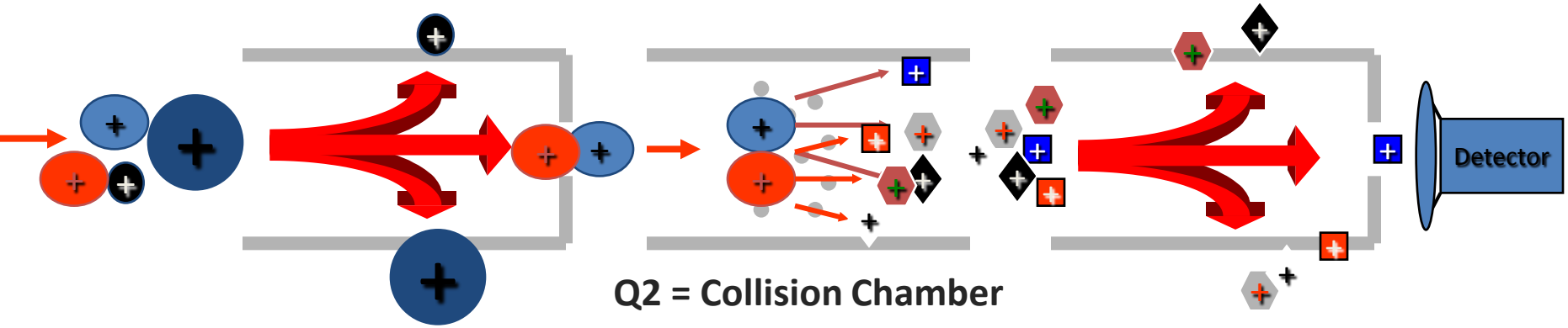
Bioanalytical rules that do not make sense! Stability testing with co-administered drugs

- Performing stability tests in the presence of co-administered drugs
  - Phase I clinical studies are rapidly moving into subject populations where the variety of concomitant medication is unknown at the start of the clinical phase
  - If you test all of the concomitant medications in plasma samples then what about their metabolites? Where does it end!
  - This is a huge amount of work for very little reward. If you're unlucky and you get that rare compound that does affect a drugs stability then you'll recognize it in the PK profile – > investigation

Bioanalytical rules that do not make sense! Selectivity Testing

- Selectivity testing of co-administered drugs when using LC-MS/MS – Same concerns that were just discussed in stability testing



A triple quadrapole instrument is an extremely powerful separation tool!

- Performing selectivity testing is a huge amount of work for very little reward. If you're unlucky and you get that rare compound that does affect a drugs selectivity then you'll recognize it in the PK profile –> investigation

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Bioanalytical rules that do not make sense! Long Term Stability

- If Long Term Stability (LTS) has been established in one lab then why do you have to prove LTS in another lab?

- Would stability in someone else's -20^{o}C freezer be different?
- What else is there to say!!!

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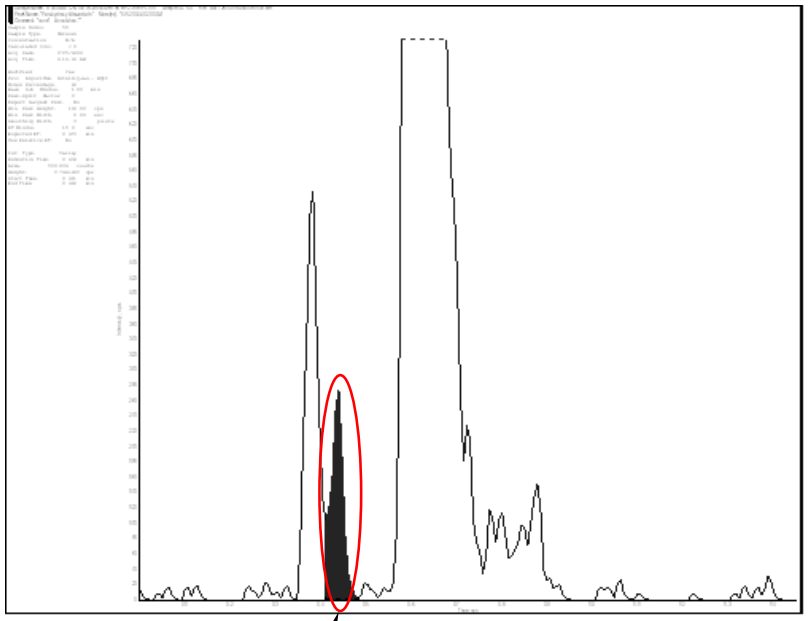
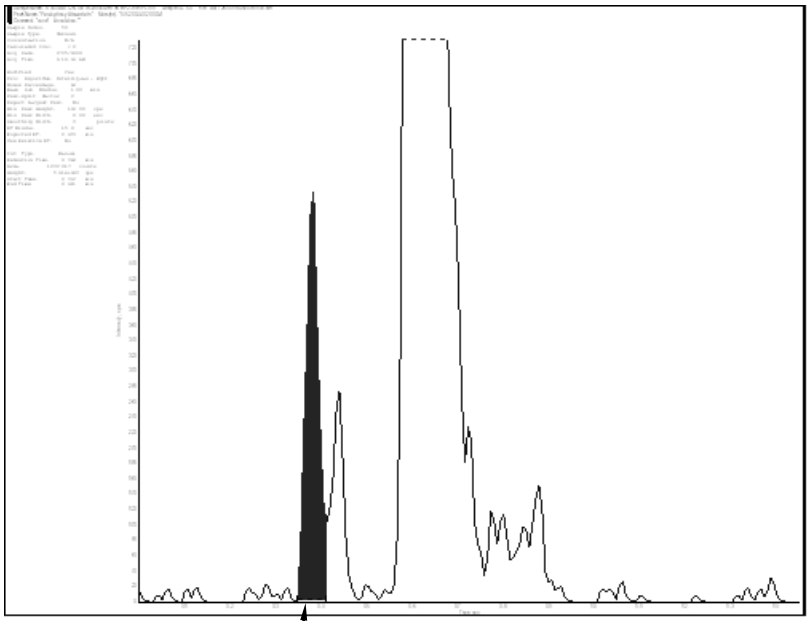
Bioanalytical rules that do not make sense! Manual integration is frowned upon

- Manual reintegration “is cheating”



Original integration, incorrect peak is integrated. (Peak area = 520.934 counts)



Manual re-integration performed to integrate correct peak. (Peak area = 1032.917 counts)

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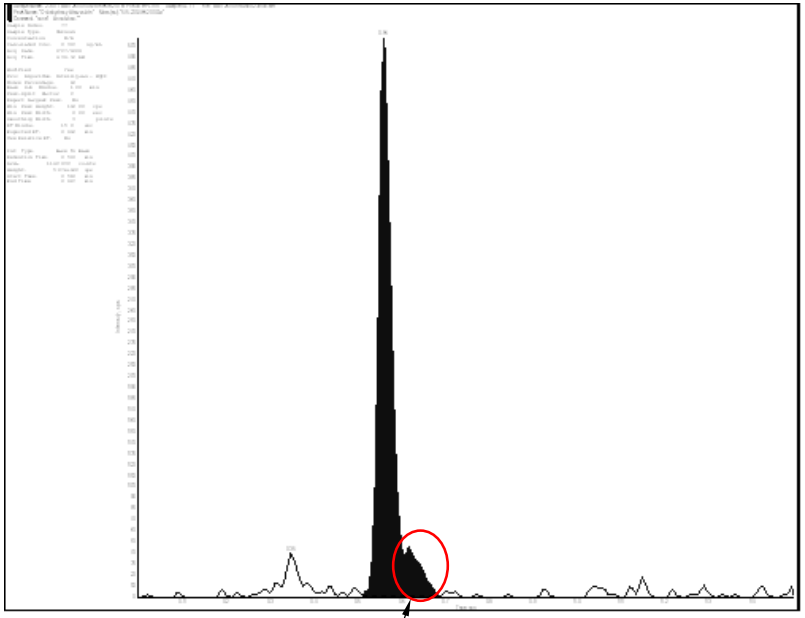
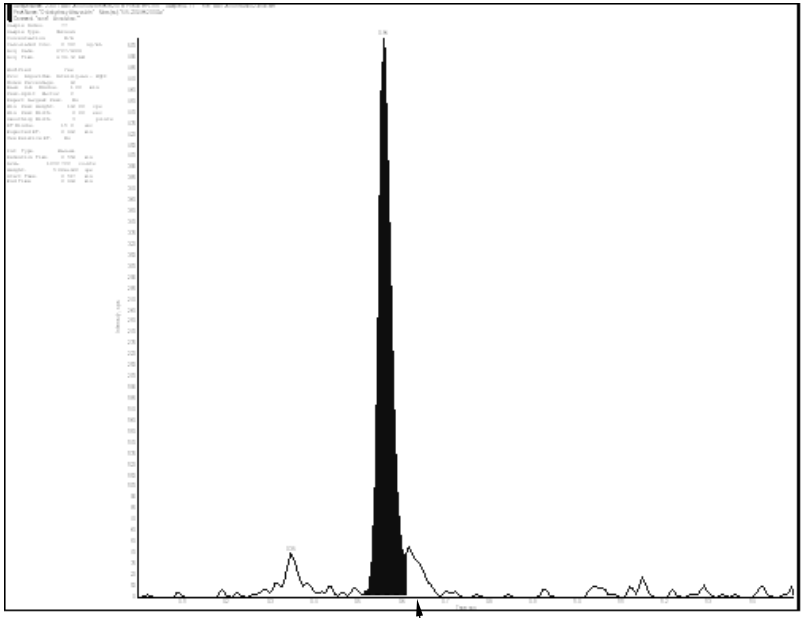
Bioanalytical rules that do not make sense! Manual integration is frowned upon

- Manual reintegration “is cheating”



Manual re-integration performed to remove tailing peak. (Peak area = 1142.932 counts)



After manual re-integration, tailing peak removed. (Peak area = 1032.722 counts)

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Bioanalytical rules that do not make sense! Manual integration is frowned upon

- Manual reintegration “is cheating”
- Obviously manual integration can dramatically improve reliability and consistency of the results
- Today most labs review and manually integrate chromatograms, lock them down and then perform regression analysis. So how can you cheat?

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Bioanalytical rules that do not make sense! Anticoagulant cations and stability

- K^2-EDTA is different than K^3-EDTA and Na^+-Heparin is different than Li^+-Heparin
  - There actually is a European Bioanalytical white paper that tested the accuracy of several drugs under these conditions – CONCLUSION = NO DIFFERENCE
  - I actually would be worried more about differences between various lots of heparin than between any differences caused by differing cations

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Bioanalytical rules that do not make sense! Reanalysis of PK samples

- Thou shall not reanalyze samples in a BE study for PK reasons
  - There was cheating in this area but that shouldn't mean that if you follow good GLP practices that it shouldn't be allowed:
    - Say what you're going to do
    - Do what you say
    - Document it!
  - Does this rule apply to BE studies submitted to CDER an CBER? I don't know!

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Bioanalytical rules that do not make sense! Freezer Mapping

- I am sure that this new requirement came from GMP stability chambers
  - Some GMP stability chambers are the size of a warehouse
  - Rule of thumb for ICH stability: 6 month stability at 40^{o}C/75% Relative Humidity = 2 years of stability at room temperature
- Therefore, there is real incentive to make sure that the GMP stability warehouses are mapped = consumer protection!
- For bioanalytical samples is there a real stability difference between -20^{o}C and -13^{o}C?
  - PK is all about comparisons – Usually the samples from the same study are stored in a similar location in a freezer. So if there was a temperature problem in the freezer most of the comparators would suffer a similar fate and the results would be OK
  - We're spending a lot of time/expense on freezer mapping and it isn't clear that it is necessary

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Bioanalytical rules that do not make sense! Event Resolution

- I wrote one of the first Bioanalytical Event Resolution SOPs in 2004:
  - "An **event** is defined as a bioanalytical issue, problem or concern that is contrary to scientific knowledge, technical experience or previous trend and that may impact the quality and integrity of the study. An event may also be a result that falls outside historical, expected or previous trends. Generally events cannot be resolved within the predefined procedures for the study by the project team."
- Then the cry arose "give me some examples!"

Bioanalytical rules that do not make sense! Event Resolution

- Examples of an event:
  - Predose sample concentration that is >LLOQ?
  - QC deviation that is >40%?
  - Etc.
- In 1964 Justice Potter Stewart (United States Supreme Court) said "**I know it when I see it**“ to describe his threshold test for pornography
- For an event “I know it when I see it” does not work today because of all the rules but in reality this is true for an experienced bioanalytical/PK person

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Bioanalytical rules that do not make sense! Recovery

- Emphasis on recovery
  - Consistent recovery across all concentration ranges makes sense, but...
  - Does it matter if stable isotopes are used as the internal standard?

Conclusion

- Bioanalytical chemistry sure has come a long way since the first guidance was published
  - The goal of creating a real-time self validating analytical process that is recognized by regulators sure hasn't been realized
- Holy #$%@! There are a lot of RULES!
- There are whole bunch of bioanalytical rules that do not make scientific sense and produce very little value for a lot of work
- The global bioanalytical community needs to stand-up and insist that nonsensical science and experiments that produce very little value need to be abolished

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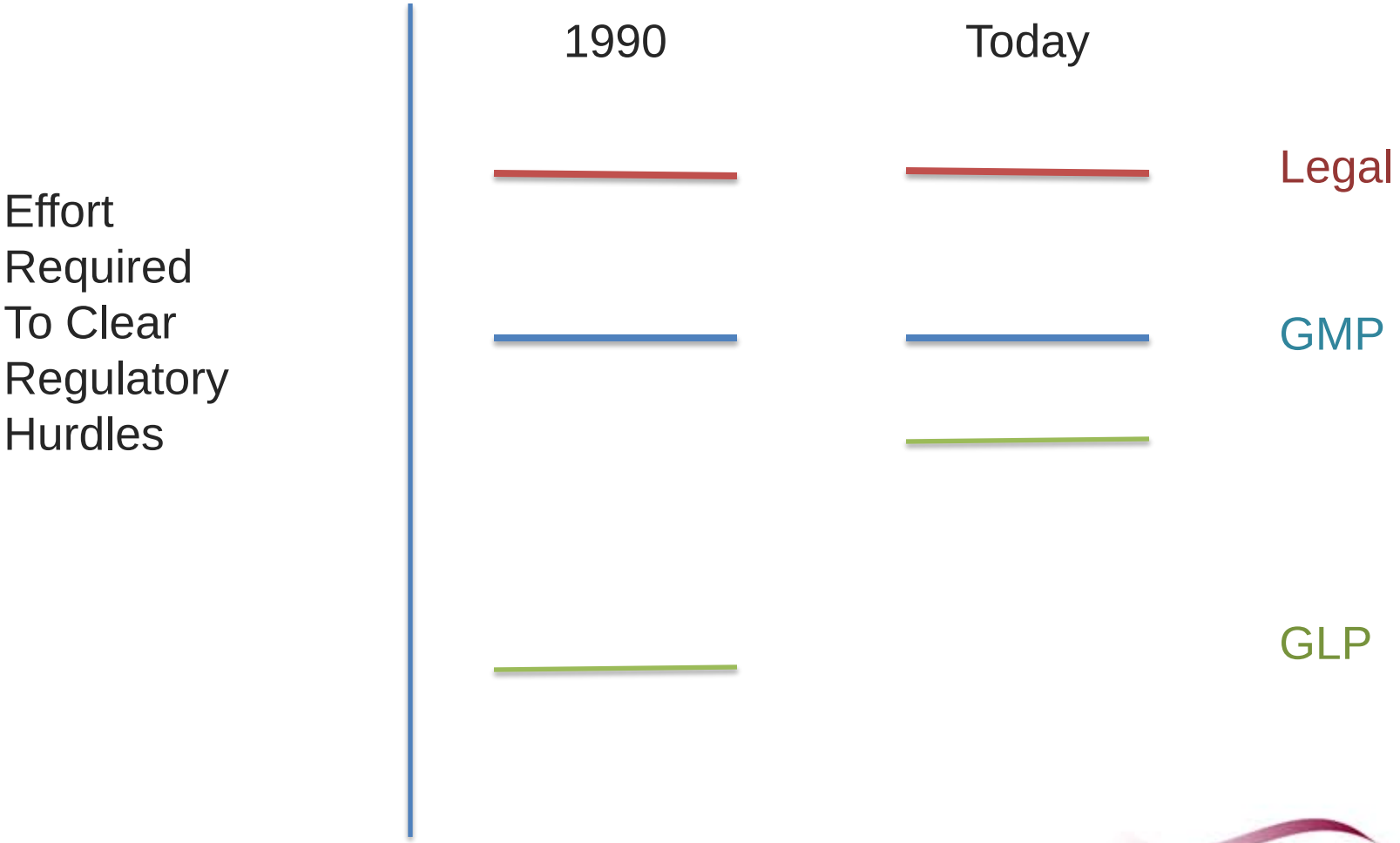
Conclusion


1990
Today
Effort Required To Clear Regulatory Hurdles
Legal
GMP
GLP