

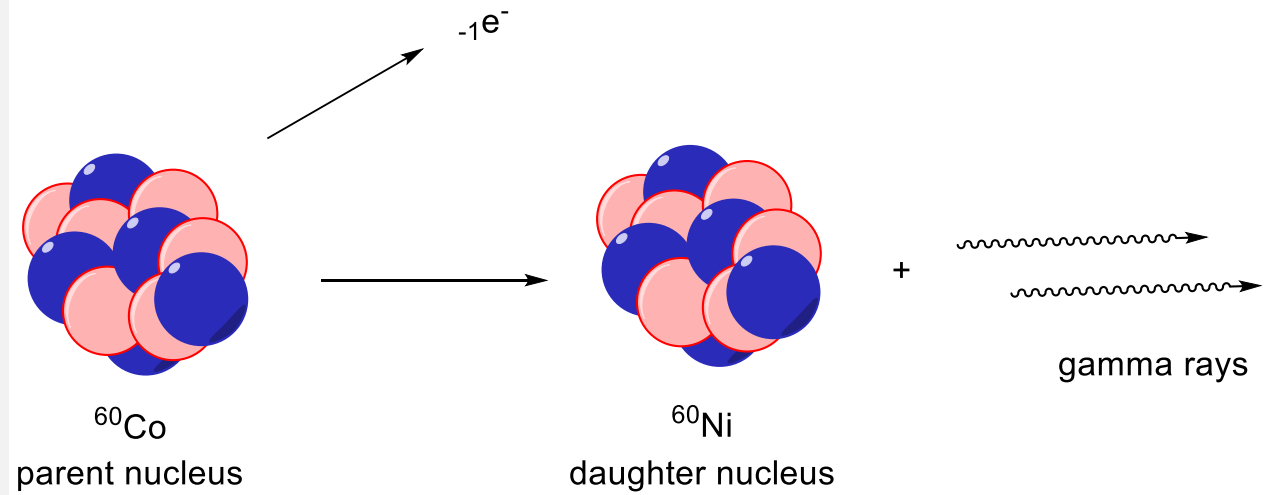


Degradation of Drug Products During Terminal Sterilization by Gamma-Irradiation

Rowan Meador

Gamma Irradiation Basics

- First appeared in *British Pharmacopeia* in 1963 and in the *United States Pharmacopeia* in 1965
- Gamma irradiation is a method of sterilization for pharmaceuticals typically using ^{60}Co source
- Has high penetration, is isothermal, and no additional chemical residues

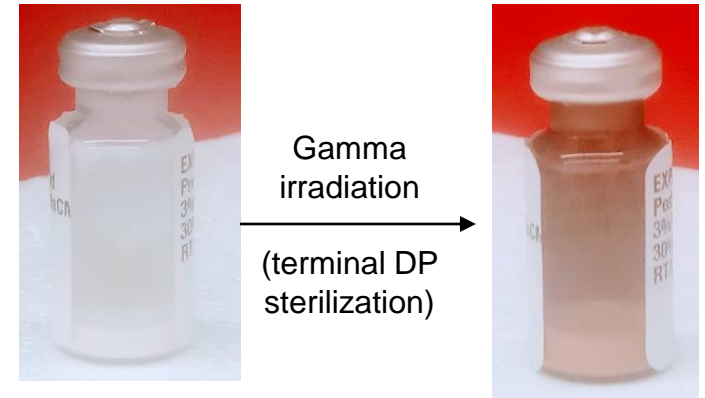


Hasanain, F.; Guenther, K.; Mullett, W. M.; Craven, E. Gamma Sterilization of Pharmaceuticals—A Review of the Irradiation of Excipients, Active Pharmaceutical Ingredients, and Final Drug Product Formulations. *PDA Journal of Pharmaceutical Science and Technology* **2014**, 68 (2), 113. DOI: 10.5731/pdajpst.2014.00955.

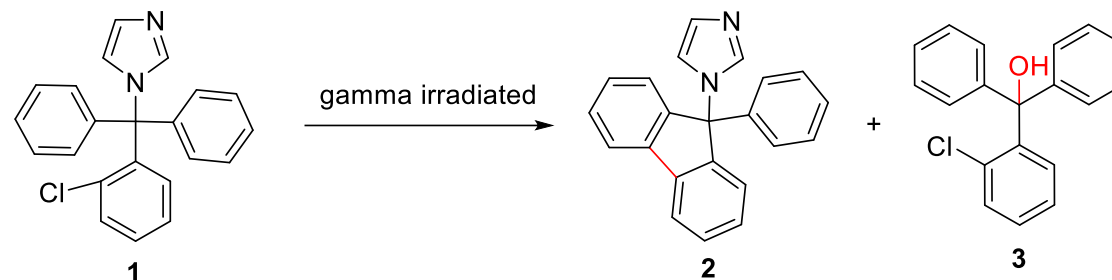
Gamma Irradiation of LAI Drug Products for Terminal Sterilization

Potential formation of novel impurities

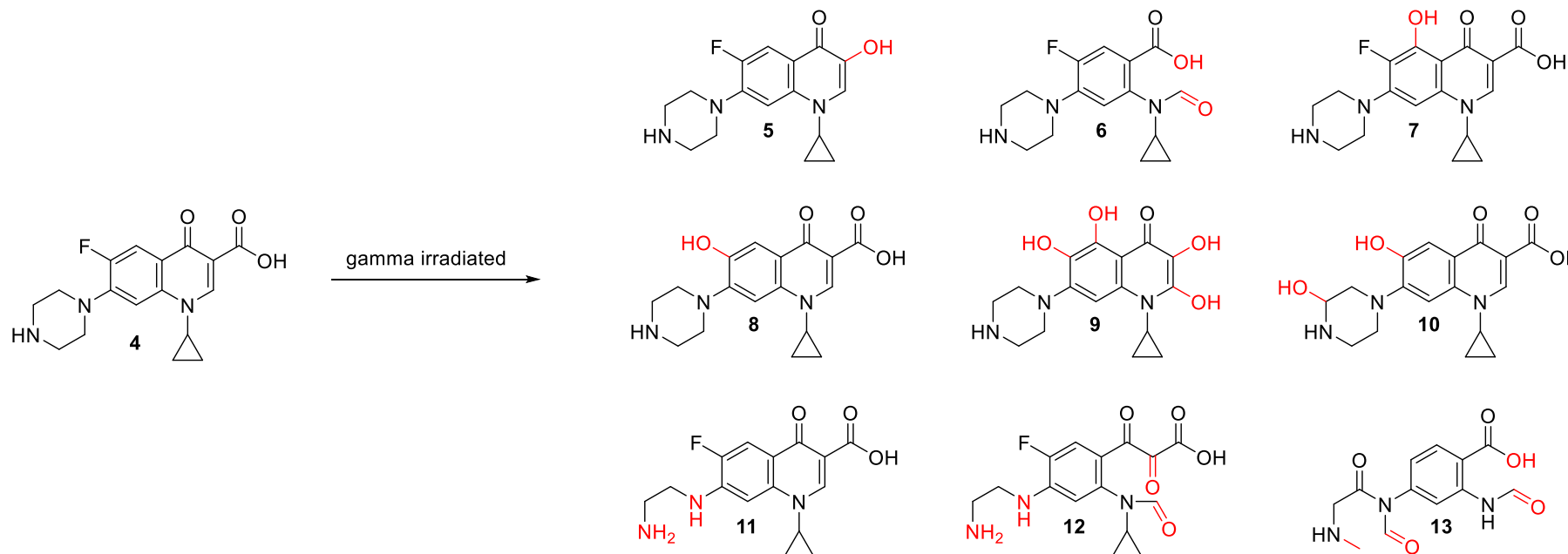
- Gamma irradiation is one of the few options available for terminal sterilization of LAI DP
 - Versus filtration, autoclaving, etc.
- Degradation of API and excipients can be induced by gamma rays, but is difficult to anticipate / predict
- The formation of novel impurities could impact analytical methods and pose risks regarding control of mutagenic impurities per ICH M7
- Understanding the impact of gamma irradiation on small molecules could aid early development of drug products



Gamma Irradiation Literature Examples



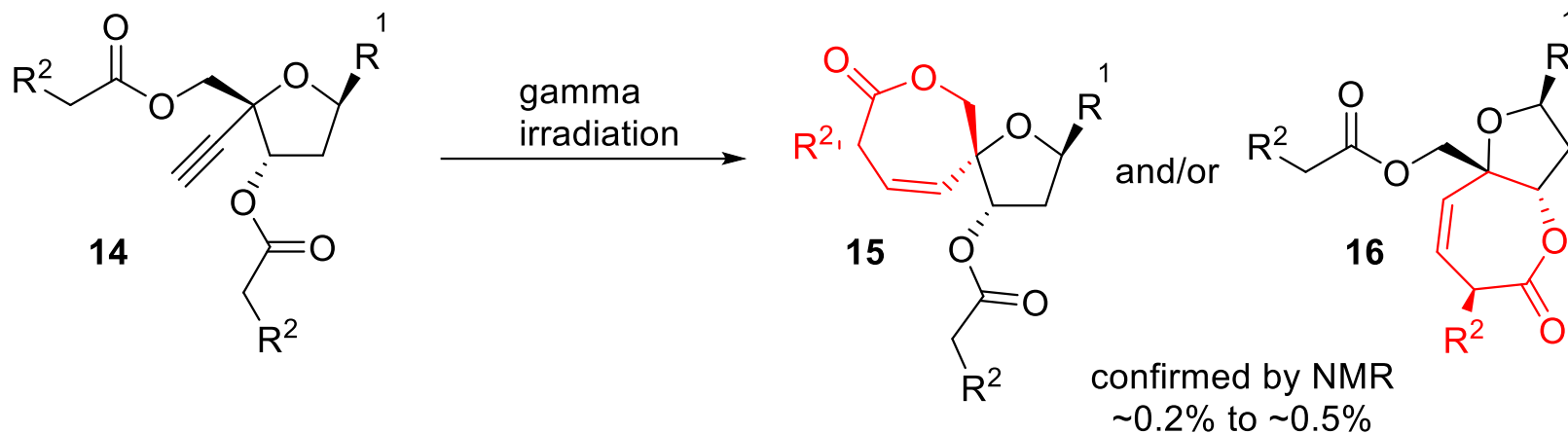
Marciniec, B.; Dettlaff, K.; Naskrent, M. Influence of ionising irradiation on clotrimazole in the solid state. *Journal of Pharmaceutical and Biomedical Analysis* **2009**, *50* (4), 675-678. DOI: <https://doi.org/10.1016/j.jpba.2008.08.032>.



Tegze, A.; Sáji, G.; Kovács, K.; Tóth, T.; Takács, E.; Wojnárovits, L. Radiation induced degradation of ciprofloxacin and norfloxacin: Kinetics and product analysis. *Radiation Physics and Chemistry* **2019**, *158*, 68-75. DOI: <https://doi.org/10.1016/j.radphyschem.2019.01.025>.

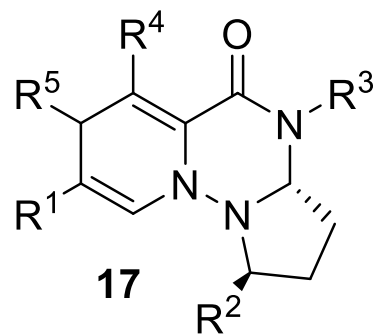
Lactone formation

Suspension drug product



N-N Bond Cleavage and Formation of Spirocyclic Ring

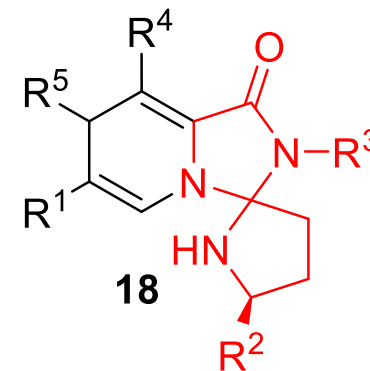
Lyophilized drug product



gamma
irradiation

observed in lyophilized DP

observed in suspension DP
but at lower levels



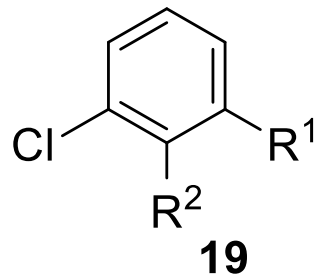
confirmed by NMR

~0.25%, and increases
on stability up to ~1%

- Impurity increases on stability
- non-gamma material does not form this impurity on stability

Dehalogenation

Lyophilized drug product

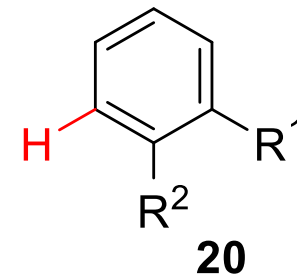


gamma
irradiation



observed in lyophilized DP

observed in suspension DP
but at lower levels

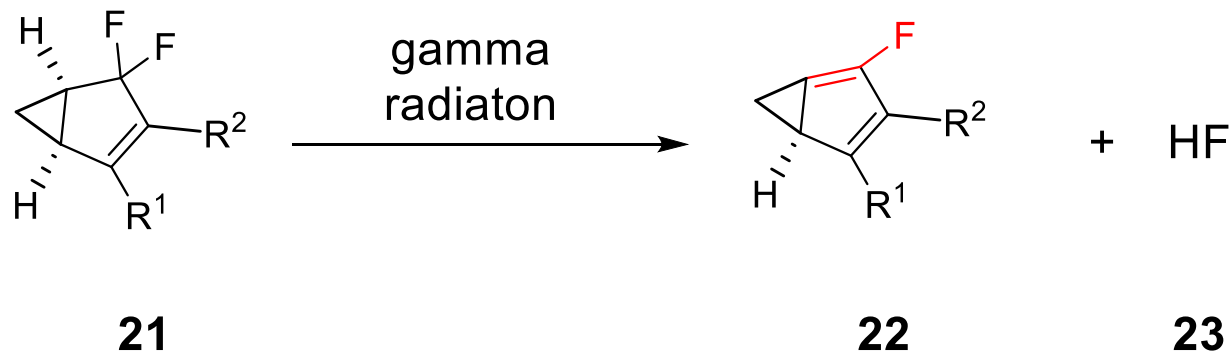


tentative by MS

~0.18%

Dehalogenation

Suspension drug product

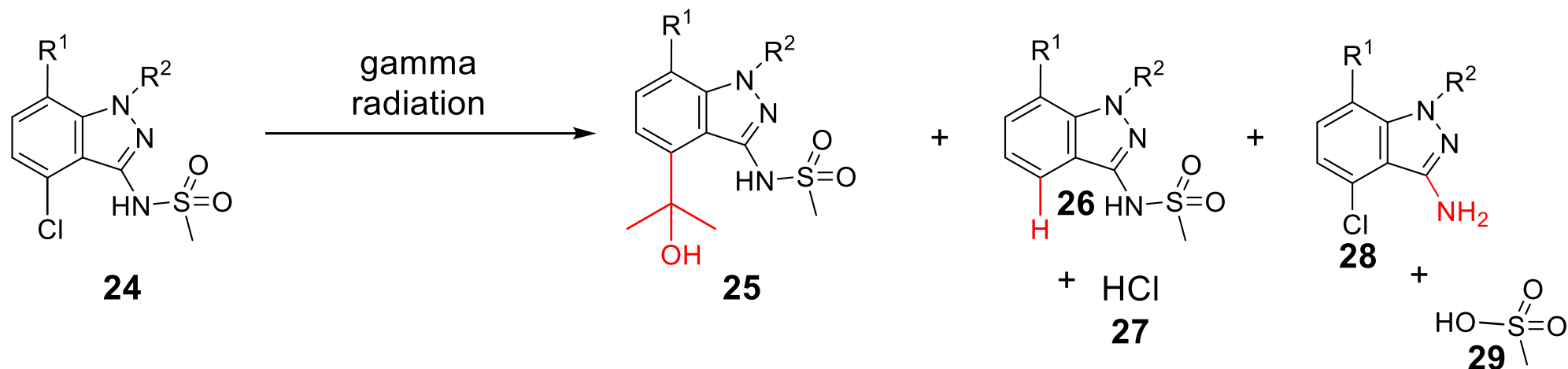


Structures
tentative by LC-
MS

- Co-elution of impurities made quantification difficult

Multiple Compounds with Same Substructure

Suspension drug product

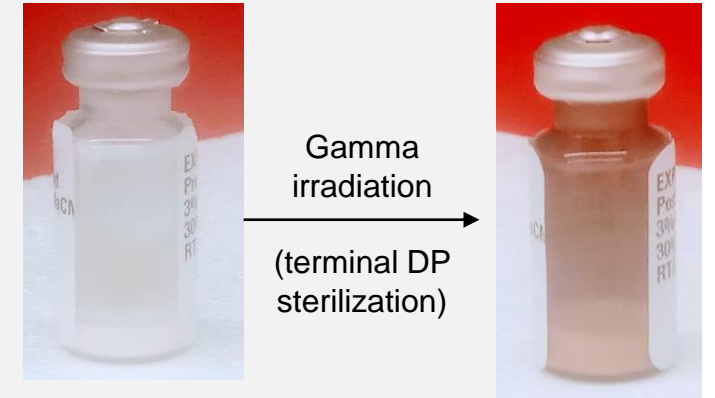


Structures tentative by LC-MS

- Co-elution of impurities made quantification difficult
- Some impurities may be formed during API milling, and not gamma-irradiation

Conclusions

- Gamma irradiation is a useful method for terminal sterilization
 - Versus filtration, autoclaving, etc.
- Gamma irradiation can generate unique products
 - These products can be difficult to predict
- Can affect different types of drug products
 - Suspension versus lyophilized
- Further studies are needed in order to understand and predict the kinds of transformations gamma irradiation can produce



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Thank you!
Any questions?

GSK

References

- Hasanain, F.; Guenther, K.; Mullett, W. M.; Craven, E. Gamma Sterilization of Pharmaceuticals—A Review of the Irradiation of Excipients, Active Pharmaceutical Ingredients, and Final Drug Product Formulations. *PDA Journal of Pharmaceutical Science and Technology* **2014**, 68 (2), 113. DOI: [10.5731/pdajpst.2014.00955](https://doi.org/10.5731/pdajpst.2014.00955).
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